

Supplement to: Corey L, Gilbert PB, Juraska M, et al. Antibody Mediated Prevention of HIV-1 Acquisition in High-Risk Populations by the Broadly Neutralizing Antibody VRC01.

This supplement contains the following items:

1. Original HVTN 704/HPTN 085 protocol, final HVTN 704/HPTN 085 protocol, summary of amendments.
2. Original HVTN 703/HPTN 081 protocol, final HVTN 703/HPTN 081 protocol, summary of amendments.
3. Original statistical analysis plan, final statistical analysis plan, final marker statistical analysis plan, summary of amendments.



PROTOCOL

HVTN 704/HPTN 085

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

DAIDS DOCUMENT ID 30095

IND 113,611 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS
Bethesda, Maryland, USA

March 9, 2016

HVTN 704/HPTN 085, Version 1.0

Contents

1	Overview	5
1.1	Protocol Team.....	8
2	Background	11
2.1	Rationale for trial concept	11
2.2	bnAbs to HIV-1	12
2.3	VRC01: VRC-HIVMAB060-00-AB	14
2.4	Trial design rationale	15
2.5	Combination Prevention for HIV acquisition.....	20
2.6	Plans for future product development and testing	23
2.7	Preclinical safety studies.....	24
2.8	Nonhuman primate (NHP) studies of VRC01	26
2.9	Phase 1 clinical trial experience	29
2.10	Potential risks of study products and administration	36
3	Objectives and endpoints	38
3.1	Primary objectives and endpoints	38
3.2	Secondary objectives and endpoints	38
3.3	Exploratory objectives	39
4	Statistical considerations.....	40
4.1	Outline of the statistical considerations section.....	40
4.2	PE parameter for the primary analysis of prevention efficacy	40
4.3	PE parameters for secondary analyses of prevention efficacy.....	41
4.4	Statistical rationale for the 3-arm design compared to a 2-arm design.....	42
4.5	Use of safety run-in data in the analyses of prevention efficacy	43
4.6	Sample size calculations for testing for overall PE (Primary objective 2) ..	43
4.7	Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group	51
4.8	Sample size calculations for safety	52
4.9	Monitoring of the trial	54
4.10	Assessment of ARV drug use	58
4.11	Randomization.....	59
4.12	Blinding	59
4.13	Statistical analyses	60
5	Selection and withdrawal of participants	73
5.1	Inclusion criteria	73
5.2	Exclusion criteria	75
5.3	Participant departure from infusion schedule or withdrawal	76
6	Study product preparation and administration	79
6.1	Study product regimen.....	79
6.2	Study product formulation	79
6.3	Preparation of study products	80
6.4	Administration	82
6.5	Acquisition of study products.....	82
6.6	Pharmacy records.....	83
6.7	Final disposition of study products.....	83
7	Clinical procedures	84
7.1	Informed consent	84

7.2	Pre-enrollment procedures.....	86
7.3	Enrollment and infusion visits	87
7.4	Post-infusion visits for HIV-uninfected study participants	88
7.5	HIV counseling and testing	89
7.6	Follow-up visits for HIV-infected participants.....	90
7.7	Follow-up visits for participants who discontinue infusions for reasons other than HIV infection.....	91
7.8	Contraception status.....	91
7.9	Urine testing	92
7.10	Assessments of reactogenicity	92
7.11	Visit windows and missed visits.....	93
7.12	Early termination visit	93
7.13	Pregnancy	93
8	HIV infection assessment and clinical response	95
8.1	HIV symptom assessment.....	95
8.2	HIV screening test (prior to randomization).....	95
8.3	HIV testing postinfusion.....	95
8.4	Endpoint adjudication.....	96
8.5	HIV infection during the study	96
8.6	Medical care for participants who become HIV infected	97
9	Laboratory.....	98
9.1	CRS laboratory procedures.....	98
9.2	Total blood volume.....	98
9.3	Assay timepoints.....	98
9.4	VRC01 mAb levels.....	98
9.5	Endpoint assays: humoral	99
9.6	ARV detection	99
9.7	Host (human) genotyping	100
9.8	Lab assay algorithm.....	100
9.9	Possible additional studies.....	100
9.10	Other use of stored specimens	100
9.11	Biohazard containment	101
10	Safety monitoring and safety review	102
10.1	Safety monitoring and oversight.....	102
10.2	Safety reporting	103
10.3	Safety pause and prompt PSRT AE review	105
10.4	Review of cumulative safety data.....	107
10.5	Study termination.....	107
10.6	Social impact reporting.....	107
11	Protocol conduct	109
11.1	Emergency communication with study participants.....	110
12	Ethical considerations	111
13	IRB/EC/RE review considerations.....	113
13.1	Minimized risks to participants	113
13.2	Reasonable risk/benefit balance	114
13.3	Equitable subject selection	114
13.4	Appropriate informed consent	114
13.5	Adequate safety monitoring.....	114
13.6	Protect privacy/confidentiality.....	115

14	Version history.....	116
15	Document references (other than literature citations).....	117
16	Acronyms and abbreviations.....	119
17	Literature cited.....	123
	Appendix A Sample informed consent form.....	136
	Appendix B Approved birth control methods for transgender men (for sample informed consent form)	153
	Appendix C Sample consent form for use of samples and information in other studies.....	154
	Appendix D Tables of procedures (for sample informed consent form).....	158
	Appendix E Sample consent form for participants with HIV infection at enrollment or during the study	159
	Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants	163
	Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants	164
	Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected.....	165
	Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection	166
	Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants	167
	Appendix K Schedule 2—Procedures at CRS for HIV-1–infected participants	168
	Appendix L Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected	169
	Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection	170

1 Overview

Title

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Primary objectives

- To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in MSM+TG
- To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in MSM+TG

MSM = men who have sex with men. TG = male-to-female and female-to-male transgender persons.

Study products and routes of administration

- VRC01: human monoclonal antibody (mAb) VRC-HIVMAB060-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered at a final volume of 150 mL intravenously (IV)
- Control for VRC01: Sodium Chloride for Injection 0.9%, USP administered at a volume of 150 mL IV

Table 1-1 Schema

			Infusion schedule (Weeks)											
			[A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80 [†]	W92 [†]
Group 1	VRC01 10 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		
	Total:	2700 (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 control)												

* Due to the randomization scheme, the numbers of VRC01 and control recipients may differ slightly.

[†] Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.

[†] Week 92 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

An interim safety assessment will be performed through the Week 24 visit for the first 450 enrolled participants. This number may include participants enrolled in the run-in in sister study HVTN 703/HPTN 081. Infusions for those 450 participants will continue while the interim safety assessment is conducted. Following enrollment of the 450th participant, enrollment can continue, subject to the following condition: No more than 25% of the total study population may be enrolled before the interim safety report is complete, reviewed by the DSMB, and submitted to the US FDA. Enrollment will then continue only if the safety record for the run-in subgroup is deemed satisfactory.

Participants

2700 HIV-1–uninfected MSM and TG who have sex with men or TG, aged 18 to 50 years, in North and South America

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

21 months of scheduled clinic visits

Estimated total study duration

56 months (includes enrollment and follow-up, including follow-up for HIV-infected participants)

Investigational New Drug (IND) sponsor

DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Study product providers

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (FHCRC) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC), FHI360 (Durham, North Carolina, USA)

Statistical and data management center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), FHCRC (Seattle, Washington, USA)

DF/Net Research (Seattle, Washington, USA)

Endpoint assay laboratories

- University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)
- Regional Network HIV Diagnostics Laboratories in South America
- Duke University Medical Center (Durham, North Carolina, USA)
- FHCRC/University of Washington (Seattle, Washington, USA)

- South Africa Immunology Laboratory, National Institute for Communicable Diseases (SAIL-NICD) (Johannesburg, South Africa)
- NIAID Vaccine Immune T-Cell Antibody Laboratory (NVITAL) (Gaithersburg, Maryland, USA)
- (NIAID) Vaccine Research Center (VRC) (Bethesda, Maryland, USA)
- HPTN Laboratory Center, Johns Hopkins University (JHU) (Baltimore, Maryland, USA)

Study sites

Clinical Research Sites (CRSs) to be specified in the Site Announcement Memo

Safety monitoring

HVTN 704/HPTN 085 Protocol Safety Review Team (PSRT); NIAID Data and Safety Monitoring Board (DSMB)

1.1 Protocol Team

Protocol leadership

<i>Chair</i>	Lawrence Corey HVTN; FHCRC 206-667-6770 lcorey@fhcrc.org	<i>Statisticians</i>	Allan DeCamp SCHARP, FHCRC 206-667-7892 adecamp@scharp.org
<i>Chair</i>	Myron Cohen HPTN; University of North Carolina 919-966-2536 mscohen@med.unc.edu		Peter Gilbert SCHARP, FHCRC 206-667-7299 pgilbert@scharp.org
<i>Cochairs</i>	Srilatha Edupuganti Emory University 404-712-1434 sedupug@emory.edu		Michal Juraska SCHARP, FHCRC 206-667-5568 mjuraska@scharp.org
	Nyaradzo Mgodli UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe 263-4-704890 nmmgodli@uz- ucsf.co.zw		Deborah Donnell SCHARP, FHCRC 206-667-5661 deborah@scharp.org
<i>Protocol Team leader</i>	Shelly Karuna HVTN Core, FHCRC 206-667-4355 skaruna@hvtn.org	<i>Medical officers</i>	Margarita Gomez Lorenzo Vaccine Research Program (VRP), DAIDS, NIAID 240-627-3510 gomezmm@niaid.nih.gov
<i>HVTN Laboratory lead</i>	John Hural HVTN Laboratory Program 206-667-1683 jhural@hvtn.org		David Burns Prevention Sciences Program (PSP), DAIDS, NIAID 301-435-8896 burnsda@niaid.nih.gov

Other contributors to the original protocol

<i>HVTN Core medical monitor</i>	Shelly Karuna HVTN Core, FHCRC	<i>DAIDS Protocol pharmacist</i>	Scharla Estep DAIDS, NIAID 240-627-3046
<i>HVTN/HPTN Consultative investigators</i>	Ken Mayer Fenway Health, Boston, USA LaRon Nelson Univ. of Rochester Rochester, NY, USA Manuel Villarán IMPACTA, Lima, Peru	<i>HVTN Regional medical liaison, Southern Africa</i>	Simba Takuva HVTN Core, FHCRC
		<i>HVTN Clinical safety specialist</i>	Maija Anderson HVTN Core, FHCRC
		<i>HVTN Statistical research associates</i>	Nidhi Kochar SCHARP, FHCRC

	Sinead Delany-Moretllwe Wits Reproductive Health and HIV Institute, Johannesburg, South Africa		Abby Isaacs SCHARP, FHCRC
<i>Product developer representatives</i>	John Mascola VRC		Jing Wang SCHARP, FHCRC
	Barney Graham VRC	<i>HVTN Social behavioral scientist</i>	Michele Andrasik HVTN Core, FHCRC
	Julie Ledgerwood VRC	<i>HPTN LOC director</i>	Nirupama Sista HPTN LOC, FHI360
<i>HVTN Laboratory Program representatives</i>	On Ho HVTN Laboratory Program, FHCRC	<i>HPTN Clinical research managers</i>	Philip Andrew HPTN LOC, FHI360
	David Montefiori HVTN Laboratory Program, Duke Univ., Durham, NC, USA		Elizabeth Greene HPTN LOC, FHI360
	Robert Coombs University of Washington Virology Specialty Laboratory, Seattle, WA, USA	<i>HVTN Clinical trials manager</i>	Carissa Karg HVTN Core, FHCRC
<i>HPTN Laboratory Center representatives</i>	Susan Eshleman HPTN Laboratory Center (LC), Johns Hopkins Univ., Baltimore, MD, USA	<i>HPTN SDMC Associate director</i>	Lynda Emel SCHARP, FHCRC
	Vanessa Cummings HPTN LC, Johns Hopkins Univ.	<i>HVTN SDMC Program manager</i>	Gina Escamilla SCHARP, FHCRC
	Estelle Piwowar-Manning HPTN LC, Johns Hopkins Univ.	<i>SDMC Project manager</i>	Evangelyn Nkwopara SCHARP, FHCRC
<i>HVTN Regulatory affairs</i>	Megan Brandon HVTN Core, FHCRC	<i>HVTN Protocol development manager</i>	Carter Bentley HVTN Core, FHCRC
<i>Clinic coordinators</i>	Debora Dunbar University of Pennsylvania, Philadelphia, PA, USA	<i>HVTN Communications unit representative</i>	Jim Maynard HVTN Core, FHCRC
	Lilian Saavedra Asociación Civil Selva Amazónica, Iquitos, Peru	<i>HVTN Community engagement unit representative</i>	Gail Broder HVTN Core, FHCRC

	Elaine Sebastian Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa	<i>HPTN Community program associates</i>	Jonathan Lucas HPTN LOC, FHI360
<i>Community Advisory Board (CAB) members</i>	Mark Hubbard Vanderbilt University Nashville, TN, USA		Jontraye Davis HPTN LOC, FHI360
	Likhapha Faku HVTN Global CAB Member at Large Rustenberg, South Africa	<i>Community educator/recruiters</i>	DaShawn Usher New York Blood Center, New York, NY, USA
	Jim Wick Bridge HIV CAB, San Francisco, CA, USA		Luciana Kamel Instituto de Pesquisa Clinica Evandro Chagas (IPEC), Rio de Janeiro, Brazil
		<i>HVTN Technical editor</i>	Erik Schwab HVTN Core, FHCRC

2 Background

2.1 Rationale for trial concept

Effective biomedical interventions are needed to reduce the acquisition of HIV. The global HIV-1 epidemic continues and while many countries have made progress toward leveling HIV prevalence over the last few years, micro-epidemics of infection continue to occur in nearly all regions, even in countries possessing the full toolkit of proven prevention approaches [1-4]. The World Health Organization (WHO) estimates that there were 2 million new HIV infections worldwide in 2014, the last year for which data are available [5].

Antiretroviral drugs (ARVs) have been shown to be effective for HIV prevention in serodiscordant couples when administered to HIV-infected individuals as treatment as prevention (TasP) and clinical trials are now underway to evaluate the efficacy of TasP at a population level [6]. ARVs have also been shown to be effective as pre- or post-exposure prophylaxis (PrEP or PEP) [7]. At present daily oral emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Truvada) is the only drug approved for PrEP use, but this drug combination has significant known side effects [8]. The requirement for daily use and the side effect profile have made adherence to this drug regimen challenging, especially over long periods of time [9]. As a consequence, the capacity of currently available ARV regimens to reduce HIV incidence or prevalence is less than optimal. Furthermore, sustained use of ARVs for HIV prevention will increase the already significant burden of ARV manufacturing and delivery for HIV treatment, especially in countries bearing the highest burden of HIV disease. For these reasons, a biomedical HIV prevention approach that exhibits sustained activity over an extended time period, that has a safety profile acceptable for healthy persons, and whose effectiveness is less dependent upon individual adherence, is still needed.

An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies, a strategy that has been employed for more than 100 years against diverse disease targets and that is still used for hepatitis A and B prophylaxis [10,11] and for PEP for rabies, measles, varicella zoster, and other infectious diseases [12]. Most notably, palivizumab has been used for respiratory syncytial virus (RSV) prophylaxis in pre-term and other high-risk infants for nearly two decades. In 1998, a multinational, randomized controlled trial showed that palivizumab administered during the RSV season reduced RSV-associated hospitalizations by 39–78% in premature infants and in children with bronchopulmonary dysplasia [13]. Subsequent studies have confirmed palivizumab's safety, efficacy, and clinical benefit for infants at high risk for RSV infection [14,15]. Hence, palivizumab serves as a model for the use of mAbs to block a mucosally-acquired infection. Significantly, passive administration of this antibody has also set a standard by which candidate RSV vaccines are evaluated, by defining antibody levels that effectively inhibit fusion by RSV. This precedent has informed the conceptual framework for this study.

Over the past several years, there has been a concerted and notably successful effort to isolate broadly neutralizing antibodies (bnAb) to HIV-1 from chronically infected donors [16-32]. Subsequent research has provided considerable insight into the sites these antibodies target on HIV-1 and their functionality (ie, the mechanisms by which they

neutralize the virus) [19,20,29,33]. This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies [34-37], prompting optimism that vaccines that elicit bnAbs against HIV-1 can be developed [35,38]. In addition, the availability of bnAbs against HIV opens the exciting possibility of antibody-mediated prevention (AMP) of HIV infection.

The Vaccine Research Center (VRC), NIAID, NIH has developed VRC01, a broadly neutralizing human mAb that targets the HIV-1 CD4 binding site [18]. This mAb was originally discovered in a participant infected with HIV-1 for more than 15 years who maintained viral control without use of antiretroviral therapy (ART) [39]. VRC01 has the capacity to neutralize a broad range of HIV-1 strains in vitro (Section 2.3) and has conferred protection against simian-human immunodeficiency virus (SHIV) challenges in nonhuman primate (NHP) studies [40-49] (Section 2.8). It has an acceptable safety profile, as seen in previous phase 1 studies (Section 2.9).

In addition to potentially developing a new HIV prevention modality, evaluating the preventive efficacy of mAbs can be expected to inform future HIV vaccine development. An important requisite for designing vaccines that elicit bnAbs is determining the level of neutralizing activity required to achieve a reasonable degree of protection in humans. It will also be important to know whether such levels vary by route of infection or neutralizing sensitivity of the infecting isolate. Notably, VRC01 contains the Fc portion of IgG1 and has demonstrated other effector functions. Evaluating the role of antibody-mediated effector functions (eg, antibody-dependent cellular cytotoxicity [ADCC], antibody-dependent cellular phagocytosis [ADCP], antibody-dependent cell-mediated viral inhibition [ADCVI], antibody-mediated virion capture in mucus, or inhibition of viral translocation across epithelial barriers, etc.) in protection is also of critical importance (see, eg, [50-53]).

Although it is not anticipated that this trial will lead directly to licensure, further assessment of this VRC01 product will depend on the results of this and other studies.

2.2 bnAbs to HIV-1

The last several years have seen a marked increase in the number of well-characterized bnAbs to HIV-1. Figure 2-1 shows the names and binding sites of many of these.

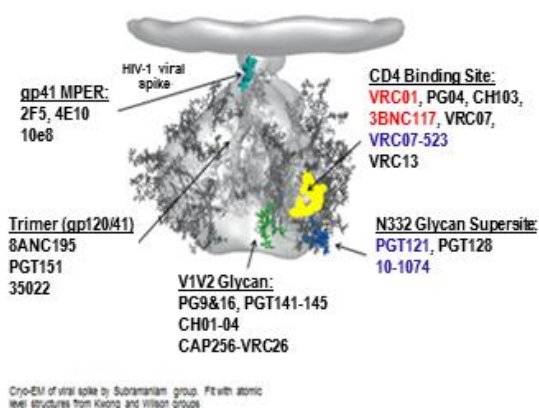


Figure 2-1 Neutralizing antibody epitopes on native Env trimer

As shown in Figure 2-2, several of these antibodies have shown considerable breadth of neutralization in in vitro testing.

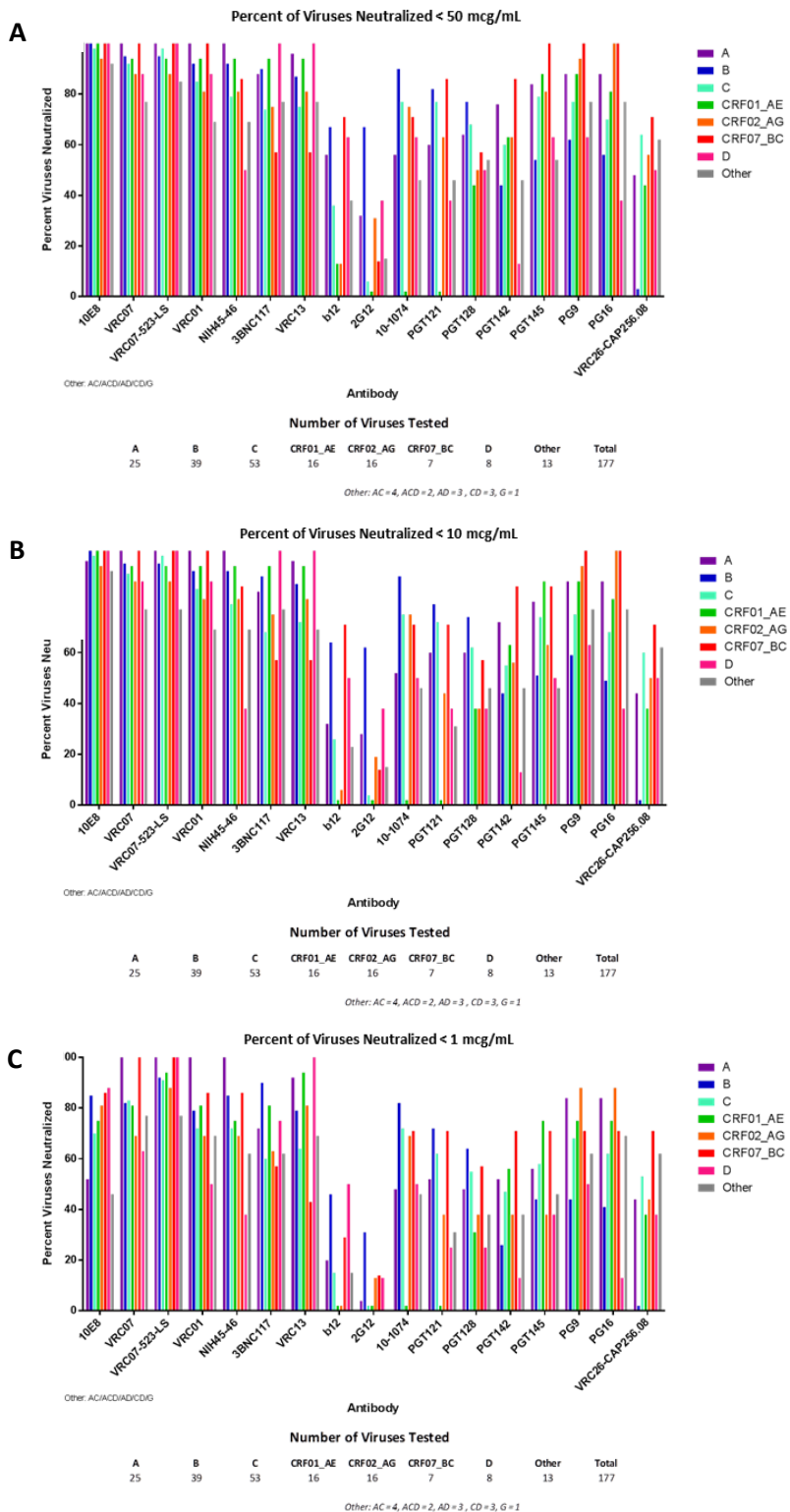


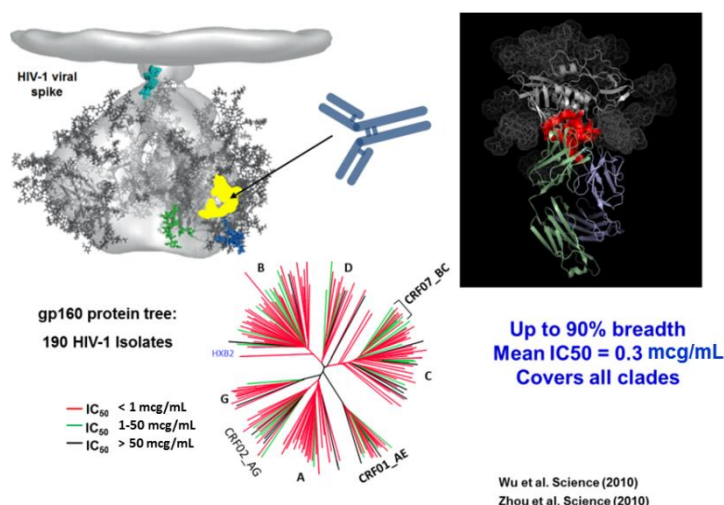
Figure 2-2 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL [32,49,54-57].

Two antibodies to the CD4 binding site of the HIV-1 envelope, VRC01 and 3BNC117 (highlighted in red in Figure 2-1), have entered phase 1 clinical trials.

2.3 VRC01: VRC-HIVMAB060-00-AB

VRC01 is a human mAb, developed by VRC/NIAID/NIH, directed against the CD4-binding site of HIV-1. The bulk lot of the drug substance was manufactured under current Good Manufacturing Practice (cGMP) conditions in a Chinese Hamster Ovary (CHO) cell line and the drug product vials were filled and labeled at the VRC Vaccine Pilot Plant (Frederick, Maryland, USA) operated by Leidos Biomedical Research, Inc. (formerly SAIC-Frederick), Frederick, Maryland (USA). Product is vialled at a concentration of 100 mg/mL VRC01 in formulation buffer containing 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. VRC01 was produced using recombinant DNA technology. Briefly, using polymerase chain reaction (PCR) amplification and cloning of the heavy and light chain variable region genes, a mAb was initially isolated from a single B cell from an HIV-1–infected subject who displayed bnAbs. VRC01 is an IgG1 antibody and is highly somatically mutated from the germ-line precursor.

The VRC01 antibody has been well characterized preclinically and has demonstrated favorable characteristics in potency and half-life [19]. In addition, it has demonstrated protection in NHP challenge studies (see Section 2.8.1 below). Figure 2-2 shows graphically the impressive breadth of VRC01, with 90% of 190 HIV-1 isolates across all clades tested showing sensitivity to neutralization by VRC01. As shown in Figure 2-3, VRC01 has a 50% inhibitory concentration (IC_{50}) of < 50 mcg/mL against 91% of primary HIV-1 isolates and IC_{50} < 1 mcg/mL against 72% of HIV-1 isolates. Notably, the IC_{50} for the vast majority of HIV-1 isolates tested is < 1 mcg/mL; the geometric mean IC_{50} for HIV-1 strains from all clades tested is 0.33 mcg/mL.



Virus clade	Number of viruses	$IC_{50} < 50$ mcg/mL	$IC_{50} < 10$ mcg/mL	$IC_{50} < 1$ mcg/mL
A	22	100%	100%	95%
B	49	96%	94%	80%
C	38	87%	84%	66%
D	8	88%	88%	50%
CRF01_AE	18	89%	83%	61%
CRF02_AG	16	81%	75%	56%
G	10	90%	90%	90%
CRF07_BC	11	100%	91%	45%
Other	18	83%	83%	78%
Total	190	91%	88%	72%

Figure 2-3 CD4 binding site antibody: VRC01 [18,19]

Details on VRC01 composition and manufacturing can be found in the investigator's brochure (IB).

2.4 Trial design rationale

Several considerations inform the design of this test-of-concept phase 2b study. The first is to establish that passive administration of bnAbs can block HIV acquisition. Based on data from in vitro neutralization studies, the NHP challenge studies described below, and pharmacokinetic (PK) data from the phase 1 clinical trials VRC 602 and HVTN 104, the doses selected are designed to elucidate the activity of the antibody across a range of serum concentrations in a diverse population of at-risk persons in multiple geographic regions of the world. The study is designed to define the optimal dosage for widespread use of the antibody or its subsequent derivatives as well as to benchmark the types of effector functions associated with efficacy, thus constituting an important bridge to other types of bnAbs and other bnAb delivery systems.

Inclusion of different doses (ie, in a 3-arm study) is important for a number of reasons. First, while the in vitro and NHP challenge data are informative, the VRC01 antibody serum level required to provide protection against HIV-1 infection in humans is unknown. Some studies suggest that transmitted-founder HIV strains may be more sensitive to neutralization than other strains (particularly by VRC01) [58,59], and therefore potentially susceptible to even lower antibody doses than those suggested by SHIV challenge studies in NHP. It must also be recognized that the lowest challenge

doses used in the NHP model likely exceed natural exposure in the majority of transmissions in humans.

Defining the lowest efficacious VRC01 dose is essential for establishing a target product profile (TPP), including optimal dosing for clinical use, for this antibody and its derivatives. Typically, higher doses of drug products are associated with lower tolerability due to side effect profiles or operational features such as length of drug administration time (eg, IV infusion time). At present the high dose (30 mg/kg) cannot be administered subcutaneously (SC), limiting the feasibility of long-term clinical use. The extreme difficulty of scaling IV administration to the populations most in need of protection against HIV infection and the complexity and cost of manufacturing mAbs would severely limit implementation of this potentially important HIV prevention tool if higher doses are required for efficacy. Therefore, it is important to evaluate the efficacy achieved at lower antibody concentrations. That lower doses of mAbs may prevent HIV acquisition is supported by the high percentage of isolates susceptible in vitro to antibody concentrations as low as 1 mcg/mL of VRC01, 1/10 the mean trough level anticipated with 30 mg/kg VRC01 dosing every 8 weeks.

Including a range of doses in this study also facilitates evaluation of antibody effector functions, in addition to neutralization, that are associated with protection (eg, virion binding, ADCC, ADCP). Note that the relationship of these important functions to neutralization is not linear and therefore cannot be inferred directly. This information will have important implications for the development of other bnAbs and other biomedical HIV prevention modalities.

Hence, in addition to providing a test of concept for AMP for HIV, if breakthrough infections are observed, the data generated by this trial will help guide development of functionally-enhanced mAbs and of long-term delivery strategies (eg, vaccine immunogen or vectored immunoprophylaxis). This trial affords a unique opportunity to correlate serum antibody levels and the potency of effector functions with protective efficacy in a trial in which these parameters can be measured close to the time of HIV acquisition, providing benchmarks for vaccine development and helping define “targets” of antibody effector mechanisms for protein or viral vector based vaccines. The data will also provide critical information by which to identify which NHP models (eg, SHIV challenge stocks) are most predictive of bnAb efficacy in humans.

2.4.1 Cohort selection

The study will be conducted among 2700 men and TG in North and South America who have anal sex with men or TG partners. The trial sample size is designed to provide 90% power to detect a prevention efficacy (PE) of 60% (rejecting the null hypothesis of 0% PE), based on reasonable assumptions regarding background HIV-1 incidence, retention, and frequency of infusions.

With respect to HIV incidence, over the past 25 years, MSM and TG who have sex with men have been the only risk groups in the US for which estimated HIV incidence has increased, with more recent increases in incidence noted particularly among young MSM of color [60,61]. In 2013, the estimated rate of new HIV diagnoses among Hispanic/Latino males was three times the rate of White males and 79% of these infections were attributed to male-to-male sexual intercourse [62]. Among gay and bisexual men, Black MSM – especially those between the ages of 13 and 24 – are most affected by HIV [63]. Indeed, the HPTN 061 study found incidence of almost 6%

annually among young Black MSM [64]; this is far higher than HIV incidence reported previously in White MSM. A second study found higher HIV prevalence in Black MSM than in White MSM [65].

We note that a parallel study assessing the safety and preventive efficacy of VRC01 is being conducted among 1500 women in sub-Saharan Africa who are at risk of acquiring HIV-1 through sexual contact. That study, designated HVTN 703/HPTN 081, will be conducted over approximately the same time period as HVTN 704/HPTN 085.

2.4.2 Dose and schedule

An equal number of study participants will be randomized to receive VRC01 mAb by IV infusion at a dose of 10 mg/kg or 30 mg/kg every 8 weeks or to receive the control by infusions every 8 weeks. The 8 week infusion interval represents approximately 4 half-lives of the study drug (half-life ~14 days based on previous clinical testing; see the IB).

Infusions will continue for 72 weeks for all groups, with a final primary follow-up visit (without infusion) at week 80 and an additional 12 weeks of follow-up without infusions. Hence, the study duration for each participant is 92 weeks, slightly over 21 months (approximately 1.75 years).

Projected serum concentrations of VRC01 are shown in Figure 2-4. This figure plots predicted median VRC01 serum concentrations over time based on PK models for VRC01 administered at 10 mg/kg every 8 weeks (Panel A) and for VRC01 administered at 30 mg/kg every 8 weeks (Panel B). The plots include shaded regions illustrating time regions where the study participants have serum concentrations in low, medium, and high ranges. Based on in vitro neutralization studies (see Section 2.3) and NHP challenge studies (see Section 2.8.1) and assuming that these accurately predict protection in humans, the expected trough levels of VRC01 are projected to be an order of magnitude higher than the levels required to protect against a majority of circulating HIV-1 strains.

See Section 2.9.3 and Figure 2-9 for VRC01 serum concentrations reported to date for participants administered 10mg/kg and 30mg/kg of VRC01 every 8 weeks in HVTN 104.

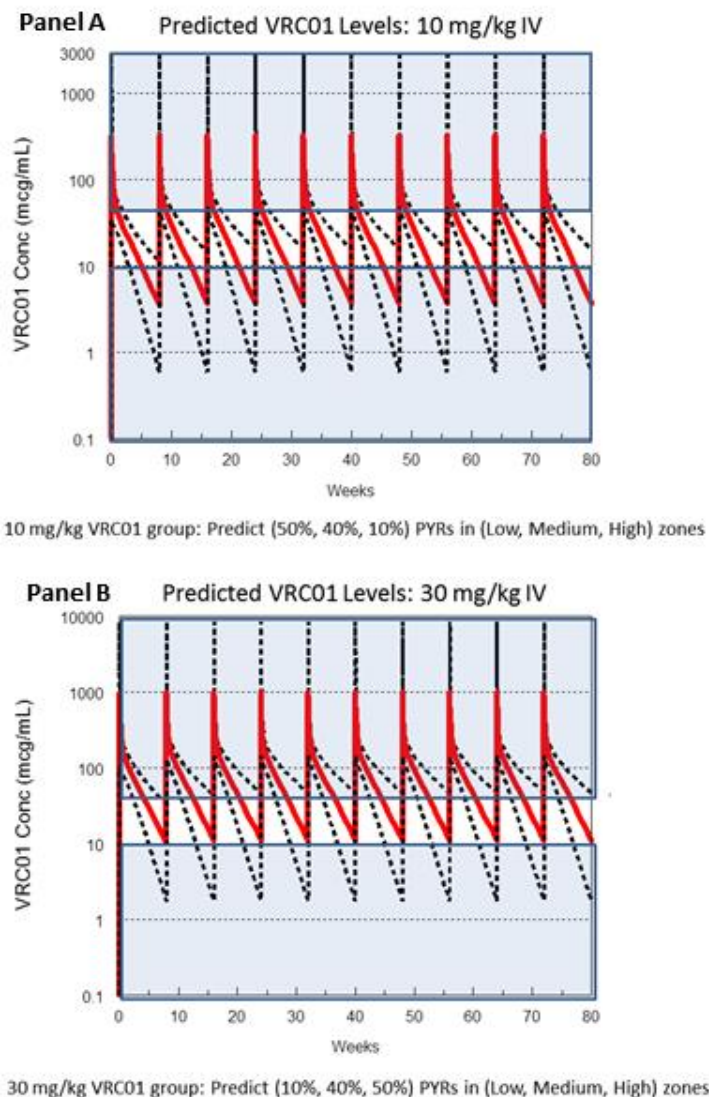


Figure 2-4 Predicted VRC01 serum concentrations over time. Panel A: Predicted VRC01 median serum concentration over time (solid lines) for 10 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72, with 95% confidence intervals (CI) (dashed lines). The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. Panel B: Predicted median VRC01 serum concentration over time for 30 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72. The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. PYR = person-year at risk.

There is a substantial overlap in the mAb concentrations between the low and high dose groups during a considerable period of time after each infusion. This is shown in Figure 2-5.

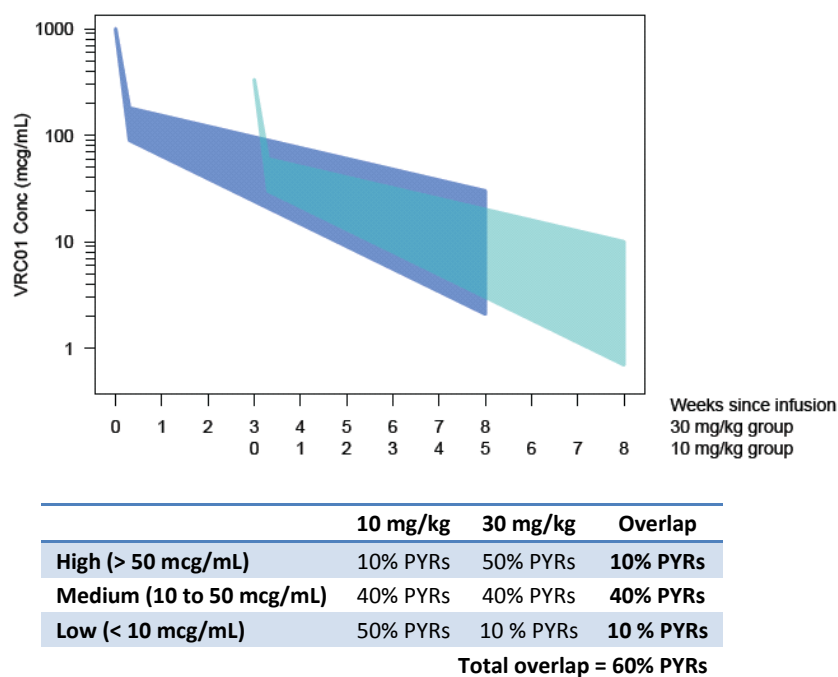


Figure 2-5 Projected overlap in serum VRC01 concentrations and PYRs of HIV exposure between high dose (30 mg/kg) and low dose (10 mg/kg) VRC01 administration

2.4.3 Choice of control

Sodium Chloride for Injection 0.9%, USP (referred to as Control) administered IV at a volume of 150 mL will serve as an inert control.

Use of a placebo control in this trial is warranted based on the scientific and public health importance of the questions it seeks to answer, the necessity of a placebo control in order to assess VRC01 efficacy in preventing HIV-1 infection, and an acceptable risk/benefit ratio considering the minimal risk associated with the placebo control selected and its administration via a procedure commonly used in clinical care. In addition, the placebo control is essential to maintain double-blinding to ensure unbiased assessments of study product safety and efficacy, and the use of the placebo control is disclosed fully to study participants (see Section 10 of Appendix A). Hence, this trial meets the standards commonly required for ethical use of placebo controls in clinical trials [66-68].

2.4.4 HIV diagnostic testing

HIV diagnostic testing will be scheduled at least every four weeks and at any time following participant report of possible exposure during the study. See Section 8 for further detail on HIV-infection assessment. Participants who are diagnosed with HIV infection after enrollment will not receive additional infusions. Infusions will also be permanently discontinued for participants who have 2 reactive HIV tests, even if subsequent testing indicated that the participant is not HIV infected.

Based on the schedule of testing, it is possible that a newly infected participant may receive an infusion of VRC01 (or Control). This does not appear to pose a safety risk for participants based on existing preclinical, clinical, and in vitro data. Specifically,

passively-infused VRC01 given to NHP on Day 7 after SHIV SF162P3 infection reduces viremia and does not cause clinical harm (see IB). Additionally, passive transfer of neutralizing antibodies (at non-protective levels) prior to infection improved control of SHIV viremia and was associated with early nAb development in infected infant macaques [69]. Furthermore, VRC01 has been evaluated in viremic and aviremic HIV-infected participants (see Section 2.9.1). VRC01 administration is associated with statistically significant transient reductions in HIV viral load in adults with chronic HIV infection (see IB), and HIV variants that escape from in vitro VRC01 neutralization have reduced viral fitness [70]. Studies evaluating VRC01 in acutely infected subjects are being initiated based on these data.

2.4.5 Trial monitoring

As this is the first large-scale phase 2b study with IV administration of a biomedical intervention for prevention of sexual HIV-1 transmission, the trial design includes an early feasibility check. After approximately 120 participants have completed the Week 32 visit, a treatment-blinded analysis of infusion feasibility will be conducted and reported to the DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq 80\%$ of those 120 participants remain engaged in the trial and have not declined further infusions. Enrollment will not be paused for this feasibility assessment, with the condition that no more than approximately 25% of the planned full study population will be enrolled prior to completion of the assessment.

In addition to the feasibility assessment, the study design includes sequential monitoring for potential harm, non-efficacy, high efficacy, and futility for assessing prevention efficacy. Following similar monitoring procedures developed and implemented for the HVTN 505 phase 2b vaccine efficacy trial, potential harm monitoring is maximally vigilant by testing for a higher HIV infection rate in the pooled mAb group versus the control group after each HIV infection and providing the results to the DSMB after each infection starting with the 20th total infection pooled over the study groups. This ensures that any potential risk of increased HIV acquisition (negative prevention efficacy [PE]) would be detected as early as possible, such that infusions of the mAb could be discontinued expeditiously. In addition, the operating characteristics of the trial (Figure 4-3 and Table 4-2) show that this potential harm-monitoring approach has a low risk of stopping the study prematurely if the true PE is 0% or higher. The non-efficacy monitoring is conducted approximately every 6 months, and is based on a trigger specified in the study monitoring plan.

At the 6-month intervals, statistical interim analysis reports are provided to the DSMB. Gilbert et al [71] describe the conceptual approach to the sequential monitoring of PE, where the implementation for the current trial is slightly different. Additional information is provided in Section 4.9. Full details regarding implementation of monitoring for this trial are contained in a separate trial monitoring plan.

2.5 Combination Prevention for HIV acquisition

Participants in all arms of the study will be provided with a comprehensive HIV prevention package consistent with all HIV prevention clinical trials. This package includes evidence-based behavioral risk reduction counseling [72], free condoms and lubricant, explanation and referral for post exposure prophylaxis (PEP) when indicated, and access to oral pre-exposure prophylaxis (PrEP, see below). These activities can be

expected to reduce HIV acquisition below historical levels for MSM. The contribution of these efforts will be monitored. Further details on these efforts are provided in the HVTN 704/HPTN 085 Study Specific Procedures (SSP) and the HVTN 704/HPTN 085 website. It should be emphasized that because the benefit of VRCO1 monoclonal antibody is unknown, subjects in each arm of the study will receive the same prevention package.

2.5.1 Evidence for PrEP efficacy

Multiple studies in multiple settings have established that daily or pericoital FTC/TDF can be highly efficacious in preventing HIV infection in MSM [7,73-77] (see Figure 2-6). In addition, evidence suggests that less than perfect adherence to a daily FTC/TDF regimen may still provide protection against infection in MSM. For example, post hoc analyses from the open label extension to the iPrEx study (iPrEx OLE) suggest that consuming 4 tablets of TDF-FTC per week is required to confer protection [73].

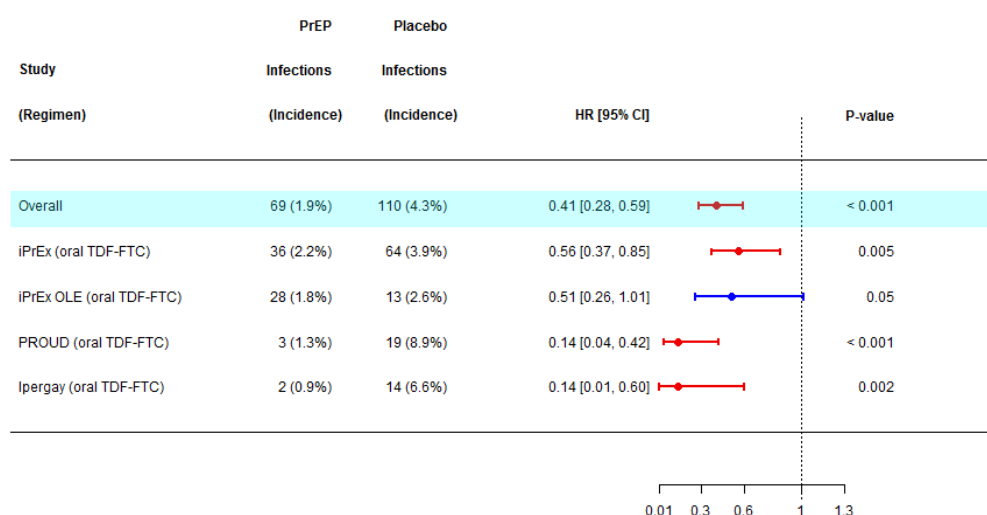


Figure 2-6 Clinical trial efficacy summary of FTC/TDF in MSM

2.5.2 Evolving PrEP guidelines

Guidelines for use of fixed dose FTC/TDF for HIV prophylaxis have evolved rapidly. In 2011, the US Centers for Disease Control and Prevention (CDC) issued interim guidelines for use of FTC/TDF as PrEP for high-risk MSM [78]. In 2012, the US FDA approved FTC/TDF for HIV prophylaxis in persons at high risk for HIV infection. That same year, the World Health Organization (WHO) issued guidance on the use of PrEP for serodiscordant couples and for men and TG women who have sex with men [79]. In 2014, the US CDC issued a further PrEP guidance document and a Clinical Provider Supplement confirming the previous recommendation of FTC/TDF PrEP as a prevention option for sexually-active adult MSM at substantial risk of HIV acquisition and expanding the recommendation to include adult heterosexually active persons at substantial risk of HIV acquisition [80,81]. PrEP has since been incorporated into WHO guidelines for ARV use for HIV treatment and prevention [82,83]; a revised and more comprehensive WHO PrEP guideline is anticipated in 2016.

2.5.3 Operationalizing PrEP access

While PrEP *efficacy* has been demonstrated and is reflected in international guidelines, PrEP's *effectiveness* depends strongly on uptake and adherence. Only 62% of iPrEx and other PrEP trial participants who were eligible to enroll in iPrEx OLE chose to do so; those who declined cited concerns about taking a daily pill and about side effects, among other reasons. Further, among those who chose to enroll, only 76% actually initiated PrEP [73]. Hence, only about 47% of those eligible initiated PrEP in iPrEx OLE. PrEP uptake would seem even less certain among individuals who have not previously chosen to participate in an FTC/TDF PrEP trial.

Limited PrEP uptake has been seen in other settings as well. In a recent PrEP demonstration project in San Francisco, Washington DC, and Miami, 60% of those eligible chose to initiate PrEP [84]; in the demonstration project PrEP Brasil, 51% of MSM elected to start PrEP [85]. Results from HPTN 073, a trial designed specifically to address open label, volitional FTC/TDF uptake and usage in 226 African American MSM in the US, are anticipated in early 2016.

Beyond experience in clinical trials and demonstration projects, questions remain about retention and adherence to PrEP in the longer term. Notably, trials of PrEP to date have been conducted among individuals specifically self-selecting for PrEP, and generally over limited time horizons.

The continued need for additional HIV prevention tools does not negate the importance of PrEP as a critical part of the HIV prevention toolkit. Accordingly, access to FTC/TDF PrEP at no drug cost will be offered as part of a complete HIV prevention package to every HVTN 704/HPTN 085 participant through a model initially developed with extensive, multi-stakeholder input for the HVTN 505 trial [86,87]. In this model, Gilead provided fixed dose FTC/TDF (ie, Truvada) at no cost to interested HVTN 505 participants, who obtained it through prescribers independent of the trial, thus facilitating the establishment of a provider-patient relationship that could endure beyond the duration of the trial. Availability of free FTC/TDF was indicated in the informed consent document and communicated to study participants in follow up visits. However, fewer than 15% of participants in the HVTN 505 trial have reported using PrEP at any time during the trial (in which follow-up remains ongoing).

The past few years have seen increasing educational efforts and community awareness of the importance of PrEP in preventing HIV infection among MSM and we expect to see increased uptake of this prevention modality over the course of this trial. For self-selected participants under active medical care, PrEP can be very effective [88].

Consistent with this approach, Gilead Sciences has agreed to provide Truvada as PrEP for trial participants at no drug cost to them for the duration of their trial participation. This will be accomplished through the HVTN 704/HPTN 085 PrEP Referral Program in North America for US participants. This program integrates PrEP into the care provided by participants' primary health care provider, ensuring that appropriate screening assays are performed and that drug interactions are monitored over time. Outside the US, participants will participate in PrEP demonstration projects in Peru and Brazil, countries in which Truvada is not yet licensed for HIV prophylaxis but where such demonstration projects are being encouraged. In this way, PrEP access will be provided to all participants in the trial and counseling about its availability will be provided as part of HIV risk reduction counseling, which is conducted at all infusion visits throughout the

course of the study. This approach has been reviewed and approved by multiple stakeholders, including community members, medical ethicists, multiple IRBs, and the HVTN 704/HPTN 085 DSMB.

As discussed in Section 9.6, periodic population-based evaluation of ARV usage will be conducted during the course of the trial using high throughput mass spectroscopy to monitor ARV usage in the study population.

The sample size and power calculations (see Section 4.6) and plans for trial monitoring by the DSMB (see Section 4.9 and, specifically, Section 4.9.3) have been designed to accommodate substantial PrEP uptake. If the background HIV incidence rate is too low to support evaluation of VRC01 prevention efficacy due to high PrEP uptake and adherence, these data will be made available to the DSMB, which will make recommendations to the team accordingly.

2.6 Plans for future product development and testing

VRC01 is considered to have potential value for both preventive and therapeutic purposes across broad geographic regions of the HIV-1 epidemic. The product was initially evaluated in phase 1 studies to characterize PK and distribution in HIV-infected and HIV-uninfected adults (VRC 601 and 602, respectively; see Sections 2.9.1 and 2.9.2) and PK and safety for multiple administrations under several route and dosing regimens are being evaluated currently (HVTN 104; see Section 2.9.3). In parallel, IMPAACT P1112 will evaluate the safety of VRC01 in high-risk infants born to HIV-infected mothers; data from this study will support a future evaluation of the efficacy of VRC01 administered to high-risk infants shortly after birth and continued through the period of breast-feeding for prevention of mother-to-child HIV transmission (PMTCT).

The development of VRC01 for clinical use depends on a number of factors, the most critical of which is the level of efficacy demonstrated by the current study. If the antibody proves to be highly effective at preventing HIV-1 infection, its development will depend on identifying a partner able to provide large-scale manufacturing. Other factors that could influence advanced development of VRC01 or similar monoclonal antibodies include: 1) the potential for improving the potency of the product to allow use at a lower dose and perhaps by an SC route, 2) the potential for increasing the half-life of the product to allow less frequent dosing, and 3) the potential to use VRC01 or its derivatives in combination with other neutralizing mAbs to increase potency and breadth of coverage. Efforts to address these issues are proceeding in parallel with the current study, but the outcome of the current study will have the greatest influence on the future clinical use of VRC01 in adult prevention or PMTCT.

2.7 Preclinical safety studies

2.7.1 Preclinical toxicology and PK study of VRC01 in rats

Table 2-1 Summary of preclinical studies

Study number	Product	Type of study	Animal	N	Dose groups	Route	Schedule
SRI No M896-11	VRC-HIVMAB060-00-AB	Repeat dose toxicity	Sprague-Dawley rats	10m, 10f each 50m, 50f total	Vehicle* 4mg/kg IV 40 mg/kg IV 400 mg/kg IV 40 mg/kg SC	IV & SC	D1, D8
SRI No M896-11	VRC-HIVMAB060-00-AB	Single-dose PK	Sprague-Dawley rats	9m, 9f each 27m, 27f total	4 mg/kg IV 40 mg/kg IV 40 mg/kg SC	IV & SC	D1

* Vehicle consists of VRC01 formulation buffer.

A repeat dose toxicity study of IV and SC administration and a single dose PK study was performed by SRI International (Menlo Park, CA) with VRC01 in male and female Sprague-Dawley rats in accordance with US FDA “Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies” (Table 2-1). This study was conducted with a pre-GMP pilot lot of VRC01 manufactured at smaller scale using a similar purification process to that of the GMP clinical grade drug product.

For the safety assessment, various doses of VRC01 (4 mg/kg, 40 mg/kg, or 400 mg/kg) or a comparable control vehicle was administered by tail vein infusion on Days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via SC administration to the dorsal scapular region on Days 1 and 8. Each group contained 10 male and 10 female rats. Five animals of each sex were sacrificed on Day 9, one day after the second administration; the remaining animals were sacrificed on Day 30, 22 days after the second administration.

Results obtained showed that both routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, infusion site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate aminotransferase (AST) and alkaline phosphatase (ALP) on Day 9. By Day 30, AST values had returned to normal, and ALP values were returning to normal.

Other than red discoloration of the administration site in one male in the SC group on Day 9, there were no other gross necropsy observations attributable to VRC01 administration. There were no histopathology findings that were considered related to IV administration of VRC01.

The pre-specified IV dose studied in rats was 400 mg/kg and SC was 40 mg/kg, which will greatly exceed the dose levels in the adult clinical studies. A “no observed effect level” (NOEL) was not determined in this study because transient elevations of AST and ALP were observed on Day 9 after IV administration and transient inflammation at the dose site was observed on Day 9 after SC administration. Because the elevated AST and ALP levels were transient and minor and did not correlate with histopathology findings,

the no observed adverse effect level (NOAEL) for VRC01 by the IV route of administration in rats was 400 mg/kg, the highest dose used in this study.

For the PK analysis, 3 groups of rats (9 males and 9 females in each group) received VRC01 on Day 1 at 4 mg/kg IV, 40 mg/kg IV, and 40 mg/kg SC respectively. VRC01 levels in serum were determined using an enzyme-linked immunosorbent assay (ELISA) with samples collected predose from each animal and from an additional 3 males and 3 females to provide untreated control serum. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following postdose timepoints: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life was about 10 days, with clearance of approximately 20 mL/day/kg and volume of distribution that was about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. VRC01 administration by the SC route resulted in mean peak serum levels at 7 days for male or 3 days for female animals. The maximum serum concentration and area under the concentration-time curve to the last timepoint values were lower when 40 mg/kg was administered by the SC route compared with the IV route. The bioavailability of 40 mg/kg VRC01 administered by the SC route was estimated to be 31.4% (males) and 42.3% (females). After the peak concentration of VRC01 was achieved in the SC group, the serum levels decreased much more rapidly from 7 to 14 days than they did in the IV groups, and VRC01 concentrations in the SC group were not quantifiable at timepoints after 14 days. These data indicate that clearance of VRC01 in rats was markedly enhanced when it was administered by the SC route. The development of anti-drug antibodies that contribute to an increased rate of clearance is often observed in preclinical safety studies of protein-based test articles when they are not tested in the species of origin. Although immunogenicity was not examined in this study, the presence of such antibodies might have contributed to the increased rate of clearance of VRC01 after SC administration that was observed in this study [89,90].

2.7.2 Tissue cross reactivity GLP study of VRC01 with human tissues in vitro

A tissue cross-reactivity study of VRC01 using normal adult and neonatal human tissues in vitro (Testing Facility Study No. A255-12) was performed by Charles River Laboratories (Reno, NV) in accordance with U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies” (GLP). The tissue panels used as the test system for this *in vitro* cross-reactivity study included all of the tissues on the “Suggested list of human tissues to be used for immunohistochemical or cytochemical investigations of cross reactivity of monoclonal antibodies” in Annex I of the “European Medicines Agency Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use on December 18, 2008” and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997).” In addition, the tissue cross-reactivity study used additional neonate/infant tissues suggested by the FDA to support future trials in infants.

To determine the cross-reactivity of VRC01 binding, VRC01 was applied to cryosections from a full panel of tissues from normal human adults and a limited panel of human neonatal tissues, immunohistochemically detected using a biotinylated rabbit anti-human IgG secondary antibody, and binding was visualized with a streptavidin-horseradish

peroxidase complex and a diaminobenzidine chromogen substrate. VRC01 binding was evaluated at concentrations of 5 and 50 mcg/mL.

Specific VRC01 staining was not observed in any normal adult human or neonatal human tissues evaluated. Therefore, in vitro evaluation of cross-reactivity in tissue specimens did not identify potential tissue sites or organ systems to more thoroughly evaluate in subsequent preclinical studies, and it supports the future use of VRC01 in humans.

2.7.3 Other toxicity studies

Several in vitro studies were conducted to assess antibody activity against self-antigens by VRC01. Several anti-HIV neutralizing mAbs will cross-react to lipid or nuclear antigens or Hep-2 cells [91,92]. Anti-lipid binding activity is understandable when considering that the HIV-1 gp41 protein is membrane-spanning and the epitopes (MPER: Membrane-Proximal External Region) recognized by some mAbs (eg, 4E10 and 2F5) are membrane-proximal and likely extend into the membrane itself. Therefore, the ability (or lack thereof) of VRC01 to cross-react with lipids was assessed in collaboration with Dr. Barton Haynes of Duke University. Binding of antibody to cardiolipin was assessed in a luminescent assay, expressed in relative units. VRC01 was compared to 4E10, an anti-gp41 mAb known to bind to cardiolipin and nuclear antigens, and Synagis, a licensed anti-RSV antibody used as a negative control. Synagis is included because it is the licensed mAb product most analogous to the intended clinical use of the VRC mAb [13].

Individual studies are summarized in Table 2-2. Unlike other anti-HIV neutralizing mAbs, VRC01 does not react to phospholipids or anti-nuclear antigens or Hep-2 cells. Additional details are provided in the IB.

Table 2-2 In vitro preclinical safety studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC01 does not react to phospholipids
Assessment of anti-nuclear antigen reactivity	VRC01 does not react with nuclear antigens
Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT)	VRC01 does not impact aPTT by binding phospholipids
Assessment of Binding to a Human Cell Line by Immunohistochemistry	Fluorescently labeled VRC01 does not bind Hep-2 cells

2.8 Nonhuman primate (NHP) studies of VRC01

Several non-Good Laboratory Practices (ie, non-GLP) studies of VRC01 have been completed in NHP to assess for preclinical evidence of potential efficacy for prevention of HIV infection. Table 2-3 summarizes the studies performed.

Table 2-3 Summary of NHP pharmacology and challenge studies

Study	Product	Animal	N	Dose/Route	Infusion schedule	Challenge route	Challenge stock/dose	Challenge schedule
Pharmacology	VRC01 (Pilot lot)	Rhesus macaques	4f 4f	40 mg/kg IV 40 mg/kg SC	Day 0	NA	NA	NA
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4m 4m 4m	5 mg/kg IV 20 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-SF162P3 (300 TCID ₅₀ *)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4f 4f	20 mg/kg IV Human IgG IV (control)	Day 0	Intravaginal	SHIV-SF162P3 (300 TCID ₅₀)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	6m 6m 4m 16m 14m	20 mg/kg IV 5 mg/kg IV 1.25 mg/kg IV 0.3 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-BaL (TCID ₅₀ 12,800 in TZM-bl)	Day 2 postinfusion

*TCID₅₀ = 50% tissue culture infectious dose

In the pharmacology study, plasma and mucosal (ie, rectal, vaginal, and nasal) samples were collected at frequent intervals through Day 28. A dose of 40 mg/kg IV or SC in female rhesus macaques resulted in plasma concentration of VRC01 exceeding 50 mcg/mL in 7 of 8 animals at Day 14 and greater than 10 mcg/mL in 7 of 8 animals at Day 28.

Please see the VRC01 IB for more details.

2.8.1 Protection against challenge in NHP models

Both neutralizing and non-neutralizing antibodies to HIV and SIV have been shown to protect against experimental challenge in the NHP model [40-42,93-97]. In these studies the degree of protection has varied with the neutralizing potency of the antibodies and with the dose, route, and sensitivity of the challenge stocks. Low antibody concentrations have in some instances been quite protective, especially against repeat low-dose mucosal challenges [44,45]. However, neutralization-resistant SHIVs have been developed and have been shown to be resistant to protection [98,99]. This has permitted estimation of neutralization titers for different mAbs against SHIVs representing a broad range of neutralization resistance.

VRC01 has been tested in several NHP challenge experiments (see Table 2-3). In a rectal challenge model with SHIV BaLP4, a dose of 20 mg/kg IV protected 6/6 NHP; a 5 mg/kg IV dose protected 6/6; and a 0.3 mg/kg IV dose protected 2/6 [47]. Using a more resistant SHIV-162P3 challenge, a 20 mg/kg IV dose protected all 4 male animals from rectal challenge and all 4 female animals from vaginal challenge [47]. Analyses of the combined data from the NHP challenge studies show complete protection against SHIV162P3 challenge at a VRC01 plasma concentration of 50 mcg/mL and partial protection (IC₅₀ [50% inhibitory concentration]) at 20 mcg/mL. For the more sensitive BaLP4 virus the IC₅₀ is only 1.5 mcg/mL. Based on preclinical studies, an antibody serum concentration of about 40 to 50 mcg/mL is projected to provide protection against the vast majority of circulating strains of HIV [100]. In the NHP studies, both the virus sensitivity and serum antibody titers appear to influence protection from mucosal challenge. A summary of serum concentrations associated with protection against diverse SHIV strains of varying resistance to neutralization is shown in Figure 2-7.

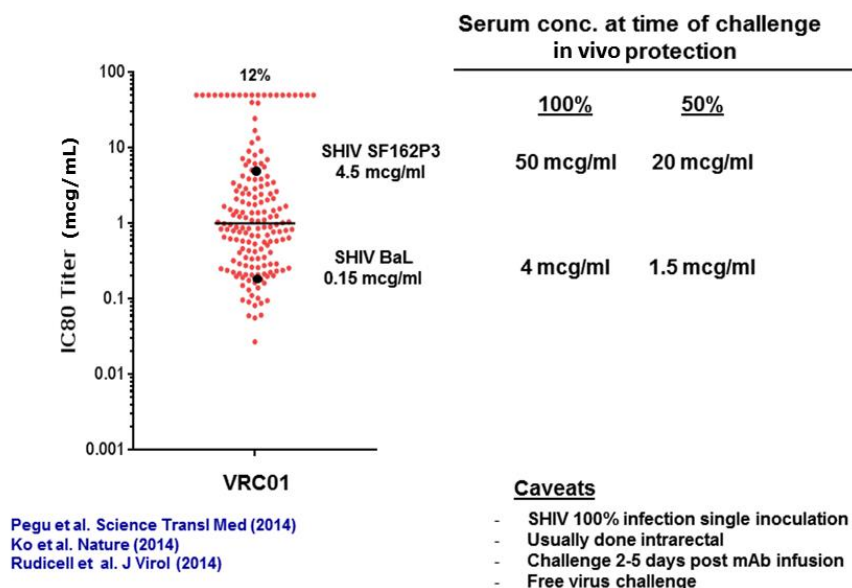


Figure 2-7 VRC01 IC₈₀ values (170 Isolates) and serum concentrations in NHP SHIV challenge studies

It is particularly interesting to note that following administration of VRC01 to NHP, the antibody is found in mucosal tissues (see Figure 2-8). This is likely a product of active antibody transport to mucosal tissues through neonatal Fc receptor (FcRn) binding [48].

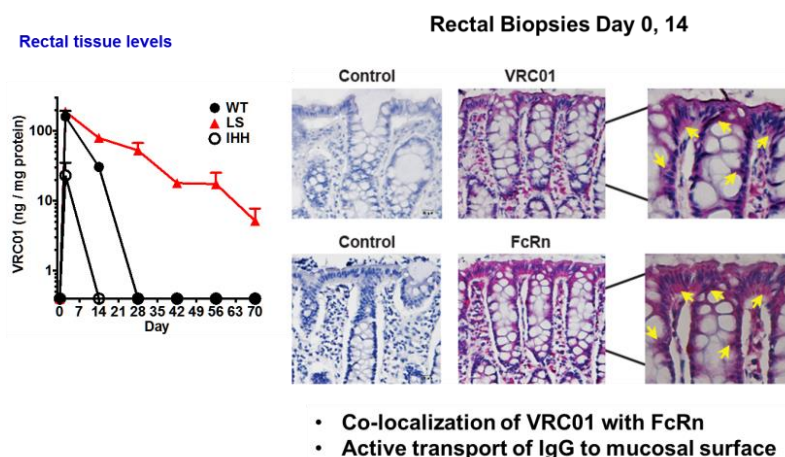


Figure 2-8 VRC01 mucosal pharmacokinetics in rhesus macaques [48]

NHP challenge studies have also shown that, in addition to classic neutralization, bnAbs such as VRC01 often elicit antibody-mediated cellular effector functions [45,101]. As a result, protection against experimental challenge has sometimes been achieved with notably low doses of VRC01 [47,100]. Similar mechanisms of protection have been implicated in studies of other bnAbs showing protection despite barely detectable neutralization activity (1:1) at challenge [44].

Recent NHP studies of VRC01 and other highly potent mAbs, such as PGT121, demonstrate protection at infusion doses of 5 mg/kg and even at 1 mg/kg [46,49,100,102]. There is also evidence that such protection can be durable; a simianized

version of VRC01 was shown to protect monkeys against SHIV challenge nearly 8 weeks after their last 5 mg/kg antibody infusion, when plasma concentrations of VRC01 ranged from ~0.5 mcg/mL to undetectable [102]. These data suggest that a 10 mg/kg infusion dose of VRC01 administered every 8 weeks may offer protection against HIV acquisition.

Please see the VRC01 IB for more details on the NHP challenge studies.

2.9 Phase 1 clinical trial experience

Phase 1 clinical trials of VRC01 are currently underway. Completed studies include first-in-humans dose escalation studies for safety, tolerability, and PK assessments in HIV-infected (VRC 601) and HIV-uninfected (VRC 602) adults. Studies to characterize the neutralizing activity and other functional assays as a function of plasma concentration are also underway.

Both the IV and SC routes of administration have been evaluated. Ultimately, the best route for clinical use may depend upon the age of the recipient (adult or infant), stage of product development, formulation, and important considerations related to volume needed and maintenance of a target VRC01 blood level considered to be in the therapeutic range.

2.9.1 VRC 601

VRC 601 (NCT01950325) titled, “*A Phase 1, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults.*”

VRC 601 (Table 2-4) was the first study of the VRC01 mAb in HIV-infected participants. It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti-antibody immune responses. VRC 601 opened in September 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and in total, 23 HIV-infected participants, including 15 aviremic ARV-treated participants and 8 viremic non-ARV treated participants, were infused with one or two doses of VRC01 at doses up to 40 mg/kg IV.

Table 2-4 VRC 601 study schema

VRC 601 Dose Groups		VRC01 Administration Schedule	
Group	No. of evaluable participants*	Day 0	Week 4
1	3-5	1 mg/kg IV	1 mg/kg IV
2	3-5	5 mg/kg IV	5 mg/kg IV
3	3-5	5 mg/kg SC	5 mg/kg SC
4	3-5	20 mg/kg IV	20 mg/kg IV
5	3-5	40 mg/kg IV	40 mg/kg IV
Total	15-25	IV doses administered in 100 mL of normal saline over 30-60 minutes. SC doses administered in the minimum volume at 15 mL/hr. *Only participants who begin infusion are evaluable. Only 3 evaluable participants per group will be enrolled into the dose group until the safety review is completed. Additional slots are available, if needed, to have sufficient data for the safety review or to include at least one eligible subject with a detectable viral load later after the dose escalation is complete.	

The first infusion at 1 mg/kg IV was administered in the VRC 601 study on September 30, 2013. Beginning on March 28, 2014, the dose escalation proceeded according to the schema. The first 40 mg/kg IV administration in this study occurred May 12, 2014 and the last infusion in VRC 601 occurred on April 6, 2015. All IV and/or SC infusions have been well-tolerated with no serious adverse events (SAEs) or dose limiting toxicity.

VRC 601 demonstrated evidence of VRC01-mediated antiviral effect. An interim analysis of the VRC 601 viral load data obtained from 8 viremic adults through April 30, 2015 shows that VRC01 has a statistically significant in vivo virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking antiretroviral therapy (ART) when enrolled into the study and had not started ART during the time period when the viral load data were collected. Six of the eight adult participants had $\geq 1 \log_{10}$ copies/mL decrease in viral load and two participants had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL respectively. These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load postinfusion days 5 to 16;
- The median time to reach $\geq 0.5 \log_{10}$ decrease in viral load is 5 days; and,
- The median time to greatest decrease in viral load is 7 days.

A 0.5 $\log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ART. To have clinical benefit, such a change would need to be sustained. In VRC 601, participants were administered only one dose of VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected. However, the data demonstrate a VRC01 mediated anti-viral effect.

2.9.2 VRC 602

VRC 602 (NCT01993706) is titled, “*A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults.*”

VRC 602 was the first study of the VRC01 mAb in HIV-uninfected adults. It was a dose-escalation study to examine safety, tolerability, dose, and PK of VRC01 [103]. VRC 602 opened in December 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and the final infusion was administered in August 2014.

As shown in Table 2-5, there were 3 open-label, dose escalation groups (Groups 1, 2, and 3) for IV administration and 1 double-blinded, placebo-controlled group (Group 4) for SC administration.

Table 2-5 VRC 602 study schema

VRC 602 Groups			VRC01 Administration Schedule	
Group	Initial Enrollments	Additional Enrollments	Day 0	Week 4
1	3	2	5 mg/kg IV	5 mg/kg IV
2	3	2	20 mg/kg IV	20 mg/kg IV
3	3	2	40 mg/kg IV	40 mg/kg IV
4	SC administration			
4A	3	2	5 mg/kg SC	5 mg/kg SC
4B	3	2	Placebo SC	Placebo SC
Total		25	20 participants treated with VRC01 at different dosage levels and 5 participants treated with placebo administered SC	
IV doses administered in 100 mL of normal saline over 1 hr.				
First SC dose administered at about 15 mL/hr via SC infusion pump; subject option for second dose administration (Week 4) by direct SC injection with needle and syringe.				

All IV and/or SC infusions were well-tolerated with no SAEs or dose limiting toxicity [103].

PK analysis from VRC 602 revealed a VRC01 terminal half-life of 15 days across all IV infused dose groups. After the first infusion, 28-day trough levels were 35 mcg/mL and 57 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. Following the second infusion, the 28-day trough values rose to 57 mcg/mL and 89 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively [103].

In addition, after infusion VRC01 retained the expected neutralizing activity in serum and no anti-VRC01 antibodies were detected [103].

2.9.3 HVTN 104

HVTN 104, titled *A phase 1 clinical trial to evaluate the safety and drug levels of a human monoclonal antibody, VRC-HIVMAB060-00-AB (VRC01) administered in multiple doses intravenously and subcutaneously in different dosing schedules to healthy,*

HIV-uninfected adults, is examining safety profiles and serum levels of 5 different regimens for the IV and SC administration of VRC01 (Table 2-6). IV administration is being evaluated at doses of 10, 20, 30, and 40 mg/kg; SC administration is being tested at 5 mg/kg.

Table 2-6 HVTN 104 study schema

Dose Groups		Study product administration schedule in months (days)											
Group	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	IV placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01
4	12	VRC01 10mg/kg IV				VRC01 10mg/kg IV				VRC01 10mg/kg IV			
5	12	VRC01 30mg/kg IV				VRC01 30mg/kg IV				VRC01 30mg/kg IV			
Total	88	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered by needle and syringe injection											

HVTN 104 is a phase 1 clinical trial designed to evaluate the safety and drug levels of VRC01 administered in multiple intravenous or subcutaneous doses and different dosing schedules to 88 healthy, HIV-uninfected adults at 6 HVTN CRSs in 4 US cities: Boston, New York, Philadelphia, and Cleveland. The first participant enrolled in HVTN 104 on September 9, 2014 and the last participant enrolled on July 15, 2015. Study product administration for all participants was complete as of November 30, 2015. The study has 5 arms: Group 1 is evaluating the IV administration of a 40 mg/kg loading dose, with 2 subsequent 20 mg/kg doses given at 8 week intervals. Groups 2, 4, and 5 are evaluating 3 infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg, respectively, given 8 weeks apart. Group 3 is evaluating 5 mg/kg given every 2 weeks subcutaneously for 24 weeks after an initial IV administration at 40 mg/kg; this will inform the design of perinatal prophylaxis studies. Secondary aims of HVTN 104 are: (1) to evaluate the kinetics of *in vitro* neutralization in serum of a single VRC01 sensitive virus isolate (TZM.bl assay); (2) to determine whether anti-idiotypic antibody (AIA) can be detected and whether there is a correlation of VRC01 levels and AIA levels in serum; (3) to determine if measurable levels of VRC01 can be found in genital, rectal, and oral secretions; (4) to evaluate the kinetics of *in vitro* neutralization in mucosal secretions of a single VRC01 sensitive virus isolate; and (5) to assess binding of VRC01 to multiple Env proteins.

A total of 249 IV infusions and 208 SC injections of VRC01 were administered in HVTN 104. The infusions and injections were well tolerated. Mild pain and/or tenderness was reported for 27% of infusions and 14% of injections, with only a single report of moderate pain and/or tenderness at 1 injection timepoint. Erythema/induration reactions were reported rarely with 1 mild and 1 moderate reaction at an IV infusion site; 2 mild

and 1 moderate reactions were reported at an SC injection site. Systemic reactions were reported by 57% of participants during the course of the trial, and most reactions were mild, with malaise/fatigue, myalgias, and headaches being the most common systemic reactogenicity symptoms reported for IV and SC administrations. Fewer than one third of participants developed systemic reactogenicity symptoms.

Severe systemic reactogenicity symptoms were reported in 3 individuals:

- 1 participant developed severe malaise, myalgia, headache and chills, mild nausea, and moderate arthralgia symptoms within 3 days after the first infusion of study product. These symptoms had resolved by Day 7. The participant had a concomitant AE of laboratory confirmed Influenza A infection diagnosed on Day 2 and was treated with Ibuprofen.
- 1 participant reported a viral illness AE of moderate intensity beginning 3 days prior to the 9th SC injection (10th study product administration), characterized by nausea and vomiting, sore throat, runny nose but no fevers; a household contact was also ill. At baseline on Day 0 of the 9th SC injection, mild malaise/fatigue was still present. At the early assessment timepoint on Day 0, this was still present and also grade 1 nausea. Within 3 days of the injection, the participant developed severe malaise, myalgia, headache, chills, and arthralgia; these all resolved on Day 6, which was the date the AE for viral illness was resolved. There was no reported use of concomitant medications for these symptoms.
- 1 participant reported severe malaise/fatigue on the day of the first infusion, resolving spontaneously the next day. During this reactogenicity period, this participant also reported a grade 1 headache on Day, resolving the next day.

There were no study product discontinuations due to reactogenicity symptoms.

Fewer than 10% of AEs reported were considered product-related and all of these were mild and transient; no SAE/EAEs have been reported. All product-related AE lab abnormalities were mild and resolved without treatment, including: increased transaminases (2 participants), increased creatinine (1 participant), and neutropenia (2 participants). Other related AEs occurring in 1 person each included injection site pruritus, Varicella zoster infection, diarrhea, chest discomfort, and generalized rash (see also Section 2.9.4). In sum, VRC01 was well-tolerated when administered IV or SC.

Of note, safety experience with VRC01 has remained consistent whether 1-2 doses were administered, as in VRC 601 and 602, or multiple doses were administered, as in HVTN 104. No trends toward recurrence of lab abnormalities or AEs deemed related to study product or increase in frequency or severity of local or systemic reactogenicity symptoms has been observed with multiple administrations of VRC01.

Figure 2-9 shows serum VRC01 levels following the first 2 infusions (samples collected as of October 19, 2015) for participants in Group 4 (10 mg/kg of VRC01) and Group 5 (30 mg/kg) of HVTN 104. The number of study participants with samples assayed at each time point is shown on the X axis of each graph. As expected, trough levels following the second infusion are somewhat higher than following the first infusion. The median antibody concentration in the 10 mg/kg group is above 10 mcg/mL for approximately 37 of the 56 days (66%) following the second infusion with a median

trough concentration of 4.6 mcg/mL (25-75% interquartile range 2.6 – 6.3). For the 30mg/kg group the median trough level is 9 mcg/mL (25-75% interquartile range 6.5 – 9.4).

These levels are quite similar to those modeled for the study and they show the desired overlap in concentrations achieved with the two doses selected for the study.

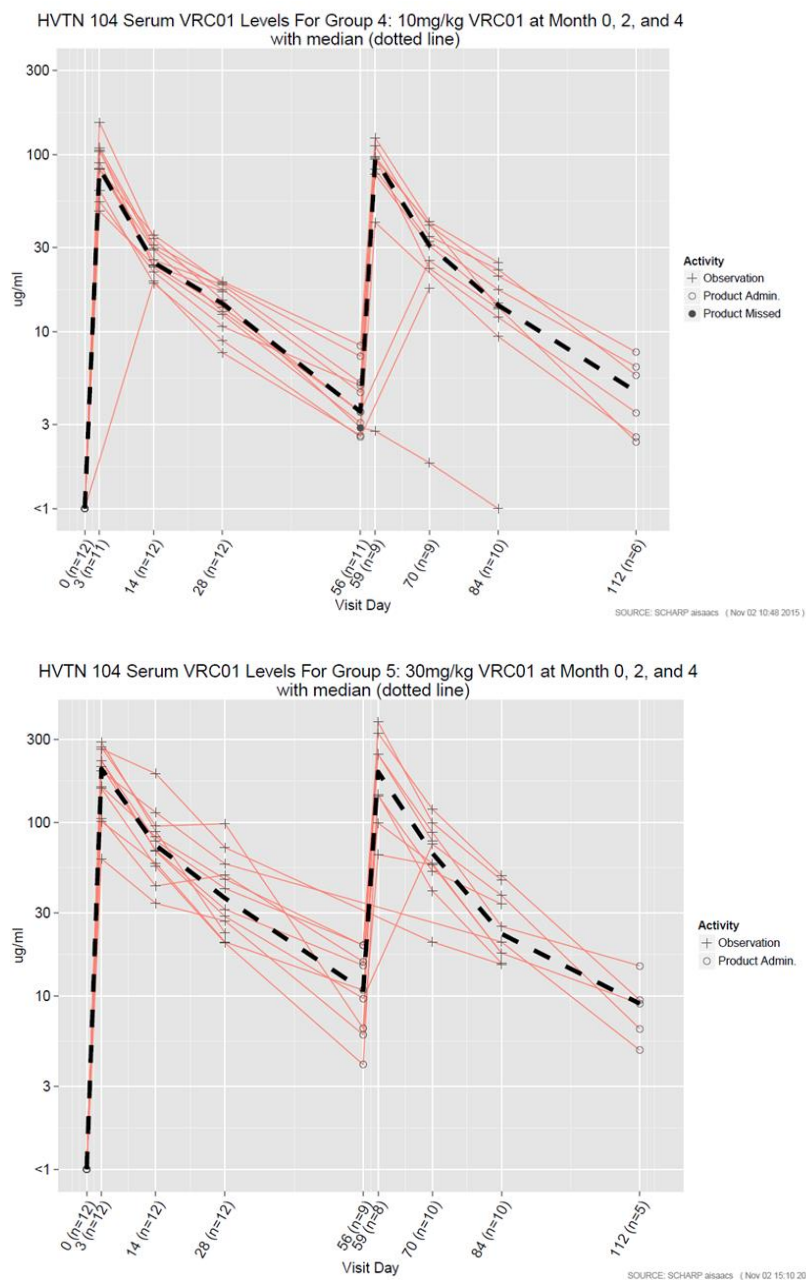


Figure 2-9 VRC01 serum levels through month 4 observed in HVTN 104 Group 4 (10mg/kg IV) and Group 5 (30mg/kg IV)

2.9.4 Safety summary of VRC01

As of February 23, 2016, approximately 130 adult participants have received one or more VRC01 administrations, including 23 in VRC 601, 23 in VRC 602 (5 additional

participants received placebo), and 84 in HVTN 104 (4 additional participants received placebo). 249 VRC01 infusions and 208 SC injections were given in HVTN 104.

Cumulatively, there have been no expedited safety reports to the FDA or study safety pauses for adverse events and no reactions during the VRC01 or placebo/control product administration that resulted in an incomplete administration.

VRC01 SC or IV administrations are generally associated with mild or moderate local reactions of pruritus, redness, and pain/tenderness, which resolve within a few minutes to a few hours after the administration is completed. When present, most systemic reactions after administration of VRC01 SC or IV are mild and include: malaise, myalgia, headache, chills, nausea, and joint pain.

Unsolicited AEs of grade 3 or higher severity and deemed related to study product have not been reported.

Other AEs attributed to study product administration have included mild or moderate AST elevation, alanine aminotransferase (ALT) elevation, creatinine elevation, and decreased neutrophil count. Mild or moderate elevated transaminases were reported in 4 of 21 (19%) HIV-infected participants in VRC 601 (all of whom were taking ARVs). These laboratory changes resolved spontaneously and did not require discontinuation of study product administration. Among HIV-uninfected participants in VRC 602 or HVTN 104, 1 participant had grade 1 (mild) transiently elevated ALT assessed as possibly attributed to VRC01 in the VRC 602 study and 2 participants had grade 1 (mild) transiently elevated ALT/AST values assessed as related to VRC01 in HVTN 104. These 3 participants all received VRC01.

In the blinded HVTN 104 trial, there have been 3 product discontinuations for AEs, 2 of which were deemed related to VRC01. One discontinuation was for a 20-minute episode of chest tightness occurring approximately 25 minutes after SC injection of VRC01 or placebo in a participant who is a chronic smoker on nicotine replacement while smoking. One discontinuation was in a participant who reported a generalized rash that began three days after SC injection of VRC01 or placebo, and resolved after a few hours with ibuprofen and the application of an over-the-counter non-steroidal cream. The third discontinuation was in a young, otherwise healthy participant who experienced a brief episode of syncope, deemed not related to study product, approximately 4 hours after IV infusion of VRC01. In addition, one person in HVTN 104 had study product discontinued due to pregnancy occurring during the trial.

Overall, VRC01 administration in the dose range from 10 to 40 mg/kg IV and at 5 mg/kg SC has been assessed as well-tolerated and safe for further evaluation.

2.9.5 Particle formation

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. In previous phase 1 studies, particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation upon thawing has no effect on product quality. For additional information, see the IB.

2.10 Potential risks of study products and administration

In a preclinical study performed in rats, there was a small dose-dependent, but transient, increase in AST and ALP, but not in ALT following IV administration. In rats, there were no histopathology findings following IV administration.

Thus far in VRC 601, VRC 602, and HVTN 104 there have been no safety concerns, including no SAEs deemed related to study product. Administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness, and the generation of auto-reactive antibodies; however, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs, which would have a risk of human anti-mouse antibodies [104]. In this regard, as VRC01 is targeted to a viral antigen and is a human mAb, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [104]; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

It is known from published experience with human mAbs directed against the cell surface targets on lymphocytes that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome [105]. Cytokine release syndrome and other immune reactions such as tumor lysis syndrome have been observed with administration of chimeric and humanized mAb [104]. Most infusion-related events occur within the first 24 hours after beginning administration. Specifically, with regard to cytokine release syndrome reactions, these most commonly occur within the first few hours of beginning the infusion and are more common with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, cytokine release syndrome is managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate [106]. Severe reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are infrequent and more often associated with mAbs targeted to human proteins or with a non-human mAb, such as a murine mAb [104].

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after exposure to the mAb and are noted to be more common with chimeric types of mAb [104]. Serum sickness has not been described with administration of licensed fully human mAbs.

There are several FDA-licensed mAbs for which reactions related to the rate of infusion have been described. Some symptoms may be treated by slowing or stopping the infusion.

Other side effects of licensed mAbs include infections, thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity [104].

The HVTN laboratory tested plasma from HIV-uninfected individuals that was spiked with VRC01 in a range of concentrations that encompasses those likely to be observed in this clinical trial. VRC01 did not cause a reactive test result using several standard antibody-based HIV-1/2 diagnostic tests used in the US. However, VRC01 is an antibody to an HIV protein, so it may be theoretically possible for a standard antibody-based HIV diagnostic test to detect VRC01 for a short time period postinfusion or postinjection. This has not been observed in clinical studies to date.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and, rarely, infection, vein inflammation (phlebitis), or blood clot.

Risks of IV Infusion: The placement of an IV catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized through the use of aseptic techniques during product preparation and administration.

3 Objectives and endpoints

3.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in MSM+TG in the Americas

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in MSM+TG in the Americas

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

3.2 Secondary objectives and endpoints

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available post-HIV-infection serum samples

3.3 Exploratory objectives

Exploratory objective 1:

To assess use of FTC/TDF and other ARVs in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF and/or other ARV use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

4 Statistical considerations

4.1 Outline of the statistical considerations section

The statistical considerations section is organized as follows. Section 4.2 states the primary and secondary efficacy objectives in terms of the target prevention efficacy (PE) parameters that are estimated in the trial, and describes the hypothesis tests regarding these efficacy parameters. Section 4.4 summarizes a statistical rationale for using a 3-arm design, which adds to the scientific rationale provided in Section 2.4. Section 4.6 describes sample size and power considerations for the primary efficacy objectives, which justify the sample size of the trial. Section 4.6 also provides operating characteristics of the trial design for addressing the primary efficacy objective. Section 4.7 describes statistical power available for the secondary objective that compares PE between the two mAb dose groups. Section 4.8 describes statistical power available for detecting safety problems of the mAb in terms of SAEs. Section 4.9 summarizes the approach to monitoring the trial including interim analysis reports provided to the DSMB. Sections 4.10, 4.11, and 4.12 describe ARV assessments, randomization, and blinding, respectively. Section 4.13 describes the approach to statistical analysis, ordered first by the approach to the analysis of PE, and secondly by the approach to the assessment of correlates of protection.

4.2 PE parameter for the primary analysis of prevention efficacy

Let PE denote the overall PE of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. This PE parameter is defined as

$$PE = [1 - \text{Cumul. incid. ratio (pooled mAb grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%,$$

where the cumulative incidence ratio is the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive the mAb divided by the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive control. PE is the target parameter for the primary analysis of overall PE.

The primary analysis tests the null hypothesis

$$H_0: PE = 0\% \text{ versus the alternative hypothesis } H_1: PE \neq 0\%$$

using a 2-sided alpha = 0.05 level test that accounts for sequential monitoring for potential harm, non-efficacy, and high efficacy.

4.2.1 Rationale for the PE parameter that measures prevention efficacy averaging over participant subgroups that access different elements of the HIV-1 prevention package

The primary PE parameter measures the efficacy of VRC01 averaging over the 10 mg/kg and 30 mg/kg subgroups, in the population-based context of study participants with different risk characteristics including host genetics, HIV-1 risk taking behaviors, and

participant decision to use different elements of the HIV-1 prevention package. The HIV-1 prevention package includes FTC/TDF PrEP, and is in harmony with the World Health Organization's November 2015 guideline on PrEP use that states "PrEP should be an additional prevention choice in a comprehensive package of services that also includes HIV testing, counseling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, voluntary medical male circumcision and harm reduction interventions for people who use drugs" [107]. The HIV-1 prevention package includes all of these elements, and study staff educate participants about the comprehensive package and facilitate access to and use of each measure. By conducting the study in a cohort of study participants who make the informed choice to use different elements of the package, the primary analysis result generalizes to a population with such heterogeneity of choice and aims to reflect efficacy in a real-world setting where such heterogeneity occurs. In particular, all study participants are counseled about the known high efficacy of FTC/TDF and are encouraged to take it. Because past experience and research has found that some individuals may prefer to not take FTC/TDF, the primary analysis conducted in a cohort reflecting such heterogeneity in prevention choices allows a representative population of individuals to participate in the trial. This approach also accommodates changes in prevention choices during the course of the trial, where the primary PE parameter is estimated in the context of these changes.

How many MSM/TG persons will initiate and adhere to fixed dose FTC/TDF when it is offered as part of an HIV prevention package is unclear; estimates vary considerably in the literature. Open label extensions of the PrEP clinical trials and reporting from the first demonstration projects of PrEP offer some insights into PrEP uptake and adherence in high risk MSM. As discussed in Section 2.5.1, uptake of PrEP has ranged from 76% in iPrEX OLE to 60% in the US-based Demo Project and 51% in PrEP Brasil [73,84,85]. While the uptake is substantial, from these studies it is also clear that a substantial fraction of high risk MSM will not initiate PrEP. Moreover, even in the context of intensive counseling, long-term adherence—especially adherence during periods of highest risk—is also unclear. It is thus most pertinent to advancing the science of HIV prevention to conduct the VRC01 primary PE analysis in a cohort reflecting heterogeneity in prevention choices, representative of the population at risk. This approach will also accommodate changes in prevention choices that emerge during the course of the trial, as the primary PE parameter will be estimated in the context of these changes.

4.3 PE parameters for secondary analyses of prevention efficacy

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall PE of the 10 mg/kg mAb group and let PE30 be the overall PE of the 30 mg/kg mAb group, defined as

$$PE_{10} = [1 - \text{Cumul. incid. ratio (mAb-10 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%$$

and

$$PE_{30} = [1 - \text{Cumul. incid. ratio (mAb-30 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%.$$

Secondary analyses test the null hypotheses

H0: PE10 = 0% versus the alternative hypothesis H1: PE10 $\neq$ 0%

and

H0: PE30 = 0% versus the alternative hypothesis H1: PE30 $\neq$ 0%

using 2-sided alpha = 0.05 level tests. Both unadjusted p-values and Holm-Bonferroni p-values will be reported for each of the individual dose versus placebo group analyses.

In addition, the following secondary analyses of PE are conducted:

- Assess a dose-response effect by testing the null hypothesis

H0: Cumul. HIV-1 incidence by 80 Wks equal in the 3 groups versus H1: $0\% \leq \text{PE}_{10} \leq \text{PE}_{30}$ with at least one strict inequality

- Test the complete null hypothesis that the HIV-1 incidence is the same in the three treatment groups versus the alternative hypothesis that there are some differences
- Test for different HIV-1 incidence between the two mAb groups, where a finding of PE30 significantly greater than PE10 would demonstrate that assignment to a higher mAb dose level causes higher PE

4.4 Statistical rationale for the 3-arm design compared to a 2-arm design

An alternative design would compare a single dose and schedule of the VRC01 mAb versus control. However, the 3-arm design allows addressing additional scientific questions and improves the assessment of correlates of protection, without requiring more participants by virtue of the primary analysis being based on the pooled mAb groups versus control. Specifically, consider a 2-arm design with 2:1 allocation to a single dose of VRC01 versus placebo, compared to the 3-arm design in the protocol with 1:1:1 allocation. For scenarios where the average of PE10 and PE30 equal PE set to a number greater than 0 and less than 1, power to reject H0: PE $\leq$ 0% in favor or H1: PE > 0% is very similar between the two trial designs, for the same total number of study participants. By providing results about estimated PE10 and estimated PE30 as well as about pooled estimated PE, the trial provides data for modeling of how PE would change given a new dose and/or schedule.

A second advantage of the 3-arm design is that it allows a direct assessment of the causal effect of different mAb infusion doses on HIV-1 incidence based on randomization of treatment assignments (a so-called 'group-level' correlate of protection), which can directly prove the concept that a higher mAb dose causes a greater level of protection. In contrast, with a 2-arm design the association between mAb marker characteristics and the level of PE can only be inferred with non-randomized epidemiological analysis approaches for which the results cannot be guaranteed to be free from postrandomization selection bias [108,109]. That is, without a randomization to multiple mAb interventions a result that a mAb characteristic is associated with reduced incidence of HIV-1 infection may not imply that mAb recipients with the characteristic have a higher level of PE. For instance, the implication may fail if participants tend to have fewer HIV-1 exposures during the few weeks after infusion visits compared to during the few weeks before infusion visits, which could possibly occur related to the counseling and informed consent process. Or, the implication may fail if the mAb characteristic marks an intrinsic

HIV-1 susceptibility factor that is not caused by administration of the mAb [110-112]. A third advantage of the 3-arm design is that the random assignment of two mAb doses creates greater inter-individual variability in mAb characteristics, which improves statistical power for the assessment of individual-level correlates of protection.

In sum, the dose-response 3-arm design has the advantages of allowing more insightful and rigorous inferences about causal effects of the mAb and greater resolution of correlates of protection, and allows addressing the additional question of whether a higher dose confers greater PE than a lower dose.

4.5 Use of safety run-in data in the analyses of prevention efficacy

Data from all participants, irrespective of enrollment into the safety run-in cohort, are included in analyses of prevention efficacy. This is valid because all enrolled participants have the same schedule for infusions and follow-up. In the event that infusions are paused, the analysis plan would be amended to censor participant follow-up more than approximately 10 weeks beyond the last infusion after the pause is instituted.

4.6 Sample size calculations for testing for overall PE (Primary objective 2)

The trial is designed to have 90% power to test

$H_0: PE \leq 0\%$ versus the alternative hypothesis $H_1: PE > 0\%$

if the level of overall pooled PE is 60% (with a 1-sided 0.025 α -level test); the design fits the paradigm of an intermediate-sized phase 2b screening efficacy trial proposed for HIV-1 vaccine efficacy trials by Rida, Fleming et al [113].

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing log-transformed cumulative incidences of HIV-1 infection by the Week 80 visit between randomized groups, in the presence of the sequential monitoring described below. Power is computed based on simulating 10,000 efficacy trials under assumptions described below using the R package seqDesign.

4.6.1 Assumptions of the sample size calculations including sequential monitoring for PE

The following assumptions are made for the sample size calculations:

- 10% annual dropout incidence in each of the three study groups
- 32 month uniform accrual with halved accrual during the first three months (approximating current accrual projections)
- visits every 4 weeks for HIV-1 diagnostic tests through Week 92
- 3% annual HIV-1 incidence in the control group
- For each of the mAb treatment groups, average PE versus control within an 8-week infusion interval is assumed to be the same for each of the 10 infusion intervals

- Sequential monitoring of the mAb groups versus control to stop early for:
 - Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring adjusted 90% CI lying below 0%]
 - Non-efficacy [Establish that PE (pooled over the mAb groups) $\leq 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
 - High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

With the exception of the potential harm monitoring, the sequential monitoring of PE does not use critical values adjusted for the number of analyses. Examination of the design operating characteristics (reported in the figures and tables below) was used to ensure that this approach provides a fitting trade-off of the control of false negative and false positive error rates.

Justification for the incidence assumptions is provided in Section 4.6.6.

We also show power calculations allowing for lower levels of HIV-1 incidence or higher levels of dropout. In particular, we show power calculations assuming 1.65% annual HIV-1 incidence in the control group, which would account for lower than expected incidence rates due to increased PrEP usage. Similarly, power calculations based on 15% annual dropout incidence are also considered.

4.6.2 Power curves and operating characteristics of the design (Primary objective 2)

Required sample sizes to achieve 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of PE are determined based on 1-sided 0.025 level Wald tests as described above. The power calculations are repeated for a range of sample sizes to determine the required sample size to achieve 90% power as reported in Figure 4-1. These power calculations are conducted using the open source R package seqDesign developed by the protocol statisticians [114], which computes power based on simulating many thousands of efficacy trials, applying the sequential monitoring procedures to each trial, and computing power as the fraction of the trials where the 1-sided 0.025-level Wald test rejects the null hypothesis. The calculations are based on a large number of simulated efficacy trials.

Figure 4-1 shows the sample size per group in the three treatment groups required to have 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of $PE = PE_{10} = PE_{30}$. The results show that about $N = 2300$ total participants are needed to achieve 90% power to detect $PE = 60\%$; the sample size $N = 2700$ total participants (900 per arm) is selected to build in a provision of robustness to the control group annual incidence being lower than 3.0%. In particular, the lowest control group annual HIV-1 incidence to retain power of at least 90% to detect $PE = 60\%$ is 2.3%.

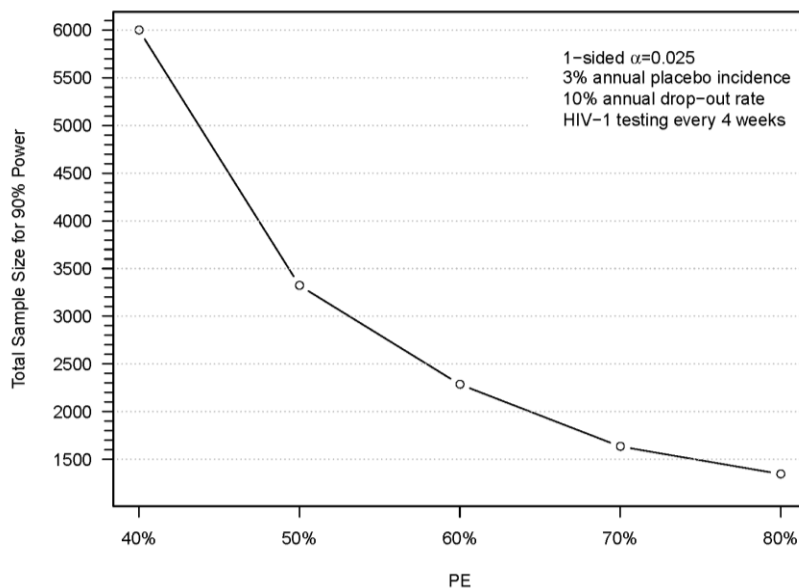


Figure 4-1 Total sample size for 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

Table 4-1 shows power available to reject the null hypothesis under different levels of true PE.

**Table 4-1 Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ under different effect sizes
 $PE = PE_{10} = PE_{30}$**

	Unconditional Power ($\times 100$)
0%	2.4
10%	7.8
20%	19.0
30%	38.6
40%	62.9
50%	84.2
60%	96.0
70%	99.5
80%	>99.9
90%	>99.9
95%	>99.9

The power calculations for the primary analysis of prevention efficacy were done assuming $PE_{10} = PE_{30}$, and it is of importance to also understand power available in the primary analysis in the event that PE_{10} differs from PE_{30} . Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ when PE equals a fixed constant PE_0 greater than 0 and less than 1 is very similar for different values of (PE_{10}, PE_{30}) subject to the constraint of average value $(PE_{10} + PE_{30})/2 = PE_0$. For example, power to test H_0 vs. H_1 is very similar for $(PE_{10}, PE_{30}) = (60\%, 60\%)$ and for $(PE_{10}, PE_{30}) = (30\%, 90\%)$. This result attains because all of these scenarios have the same number of expected HIV-1 infection events among study participants assigned to receive VRC01. Power tends to be slightly greater for differential scenarios like $(PE_{10}, PE_{30}) = (30\%, 90\%)$ compared to the equal scenario $(PE_{10}, PE_{30}) = (60\%, 60\%)$, because the hypothesis testing procedure stratifies by VRC01 dose group, gaining efficiency by accounting for a baseline variable that predicts HIV infection. Therefore, the trial is powered to detect the design alternative

of a dose-pooled VRC01 efficacy PE equal to 60%, regardless of whether VRC01 efficacy differs by dose group.

4.6.3 Additional operating characteristics of the design for assessing primary objective 2

For the selected sample size ($N = 2700$), Figure 4-2 shows the power curves for rejecting $H_0: PE \leq 0\%$ in favor of $H_0: PE > 0\%$ for a range of fixed values of the pooled PE. The power for rejecting H_0 when the HIV-1 incidence rate is lower than projected or dropout rate is higher than projected are included in the figure.

The scenario of 1.65% annual HIV-1 incidence represents various amounts of PrEP use among study participants. In particular, this 1.65% assumption is attained if 50% of person-years at-risk are not during PrEP use with annual incidence of 3.0%, and the other 50% of person-years at-risk are during PrEP use at PrEP efficacy of 90% and hence with annual incidence of 0.3% [$1.65\% = (3.0\% + 0.3\%)/2$]. In addition, a slightly higher control group annual incidence of 2.0% is attained under each of the following three scenarios, all of which assume 90% PrEP efficacy during PrEP use and 3% annual HIV-1 incidence during person-years at-risk without PrEP use: (A) 50% of person-years at-risk during PrEP use in the U.S.; 25% in Peru and Brazil; and 69% participants enrolled in the U.S.; (B) 60% of person-years at-risk during PrEP use in the U.S., 30% in Peru and Brazil, and 61% of participants enrolled in the U.S.; (C) 75% of person-years at-risk during PrEP use in the U.S., 40% in Peru and Brazil, and 48% of participants enrolled in the U.S. These calculations support that the study has adequate power to meet the primary efficacy objective if there is substantial PrEP use.

Moreover, we also conducted power calculations assuming 50% of person-years at-risk during PrEP use in all three countries, which means that the overall annual HIV-1 incidence in the placebo group is 1.65% [$= (3.0\% + 0.3\%)/2$]. In this scenario, the trial has 78% power to detect $PE = 60\%$.

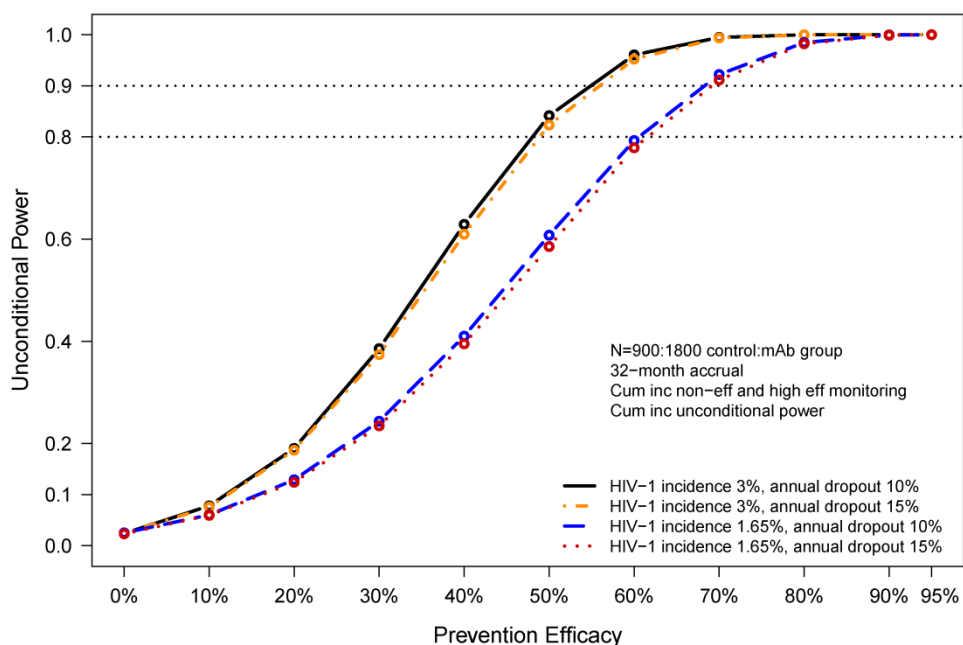


Figure 4-2 Unconditional power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for a range of fixed values of pooled PE based on primary assumptions for HIV-1 incidence and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.6.4 Additional operating characteristics of the primary analysis accounting for the sequential monitoring

For the selected sample size ($N = 2700$), Figure 4-3 shows probabilities of reaching each possible trial monitoring outcome, pooling over the two mAb treatments (under the primary assumptions about HIV-1 incidence and dropout rates). More specifically, the monitoring outcomes include potential harm, non-efficacy, and high efficacy. Table 4-2 provides the same information in tabular form. In addition, the figure and table show unconditional power in the primary analysis to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$.

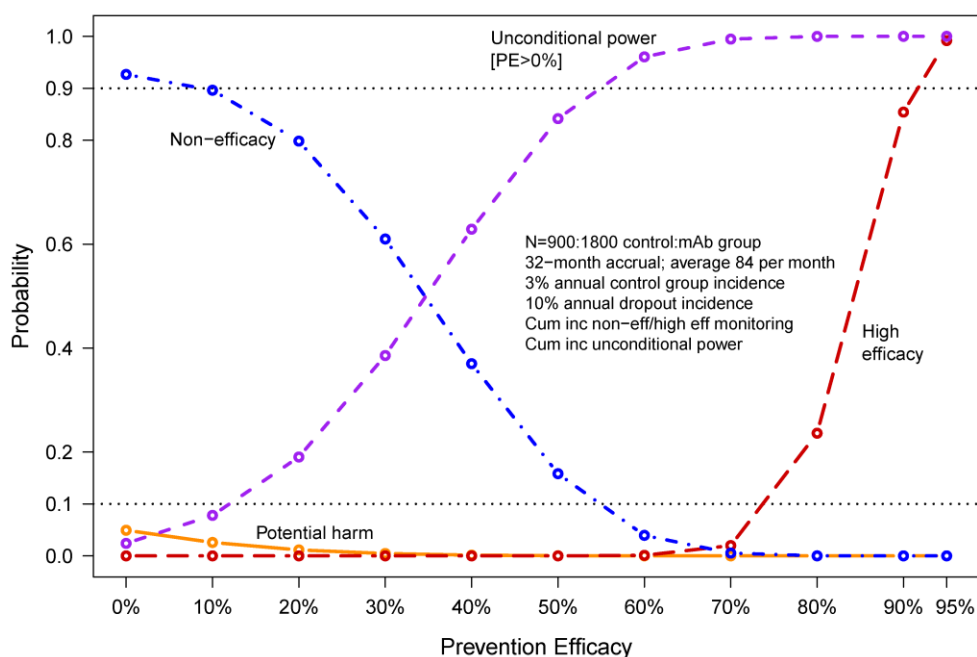


Figure 4-3 Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the primary null hypothesis $H_0: PE \leq 0\%$ with 900 control recipients and 1800 mAb recipients (1-sided 0.025-level tests)

Table 4-2 Probabilities (x 100) of reaching each possible trial monitoring outcome, and unconditional power (x 100) to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups (1-sided 0.025-level tests)

PE	HR	Weed Out at Interim Analysis			Unconditional Power PE > 0%
		Potential Harm PE < 0%	Non-Efficacy PE < 40%	High Efficacy PE > 70%	
	3.0	95.3	4.7	0.0	0.0
	2.5	87.8	12.2	0.0	0.0
	2.0	69.1	30.9	0.0	0.0
	1.5	34.0	66.0	0.0	0.0
0%	1.0	4.9	92.7	0.0	2.4
10%	0.9	2.6	89.6	0.0	7.8
20%	0.8	1.1	79.8	0.0	19.0
30%	0.7	0.4	61.0	0.0	38.6
40%	0.6	0.1	37.0	0.0	62.9
50%	0.5	0.0	15.8	0.0	84.2
60%	0.4	0.0	4.0	0.1	96.0
70%	0.3	0.0	0.5	2.0	99.5
80%	0.2	0.0	0.0	23.6	100.0
90%	0.1	0.0	0.0	85.4	100.0
95%	0.0	0.0	0.0	99.2	100.0

N = 900:1800 Control:mAb group

3% annual incidence in the Control group

10% annual dropout

Cumulative incidence-based non-efficacy monitoring

Cumulative incidence-based high-efficacy monitoring

Cumulative incidence-based unconditional power

Table 4-3 shows the numbers of HIV-1 infection endpoints during the trial expected under the null hypothesis scenario PE = PE10 = PE30 = 0% and under the design alternative hypothesis scenario PE = PE10 = PE30 = 60%. Under the design alternative hypothesis scenario, the calculations show that 37 HIV-1 infection endpoints are expected in the control group and 30 HIV-1 infection endpoints are expected in the two mAb groups combined after 80 weeks of follow-up.

Table 4-3 Cumulative number of HIV-1 infection endpoints over 80 weeks of follow-up under the null hypothesis scenario $PE_{10} = PE_{30} = 0\%$ and under the design alternative hypothesis scenario $PE = PE_{10} = PE_{30} = 60\%$. Medians are computed based on simulating a large number of efficacy trials.

$PE_{10} = PE_{30}$	Weeks since first person in	Median number of control endpoints	Median number of pooled mAb group endpoints
0%	0	0	0
0%	26	0	1
0%	52	3	7
0%	78	9	18
0%	104	16	32
0%	130	22	45
0%	156	25	50
0%	182	26	54
0%	208	26	55
0%	210	26	55
60%	0	0	0
60%	26	0	0
60%	52	3	3
60%	78	9	7
60%	104	16	13
60%	130	23	19
60%	156	30	24
60%	182	35	28
60%	208	37	30
60%	219	37	30

4.6.5 Power curves for secondary hypothesis tests about PE in each mAb group

Figure 4-4 shows unconditional power to reject the null hypothesis $H_0: PE_{10} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{10} > 0\%$ (or, equivalently, the null hypothesis $H_0: PE_{30} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{30} > 0\%$), where PE_{10} and PE_{30} measure prevention efficacy in each mAb group separately.

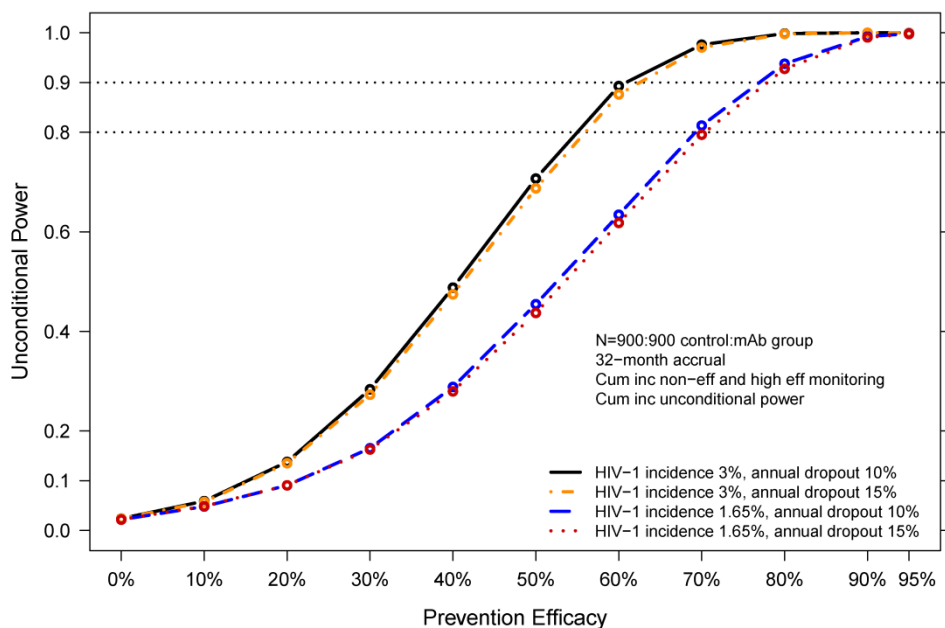


Figure 4-4 Unconditional power to reject H_0 : $PE_{10} \leq 0\%$ in favor of H_1 : $PE_{10} > 0\%$ (or H_0 : $PE_{30} \leq 0\%$ in favor of H_1 : $PE_{30} > 0\%$) based on primary assumptions about HIV-1 incidence rate and dropout rate (1-sided 0.025-level tests). Power curves are also shown for lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.6.6 Rationale for the HIV-1 incidence assumptions

The assumption of 3% annual HIV-1 incidence in the control group accommodates background PrEP use by assuming incidence is decreased by two parameters: (1) the fraction of person-years at-risk during which PrEP is used; and (2) the level of efficacy of PrEP during PrEP use. Figure 4-5 shows the annual HIV-1 incidence in the control group as a function of these two factors, for a scenario where the annual HIV-1 incidence is 4% in the absence of any PrEP use. Based on HVTN 505 data (US participants only) through September 30, 2014, the annual HIV-1 incidence in the control group was 2.0% (95% CI 1.5%–2.7%) and in the vaccine and control groups pooled was 2.1% (95% CI 1.5%–2.8%). From HVTN 505, based upon case report form collection of PEP/PrEP med usage and responses to questions regarding usage posed on the ‘anonymous’ (to the site) ACASI questionnaire through June 1, 2014, 5% of participants reported ever using PrEP. In HVTN 505 the amount of person-years at risk during periods of PrEP use was likely well below 5%, and, therefore, the 2.1% annual incidence is a reasonable assumption for the baseline rate without PrEP. In particular, assuming 1.6% annual control incidence in the US (which is expected if 27% of person-years at risk are during PrEP use and PrEP efficacy is 90% during use) and assuming 5% annual control incidence in South American participants [7], (with 5% of person-years at risk during PrEP use and 90% PrEP efficacy during use), 44% of participants enrolled at South American sites would yield the assumed 3% annual control incidence rate.

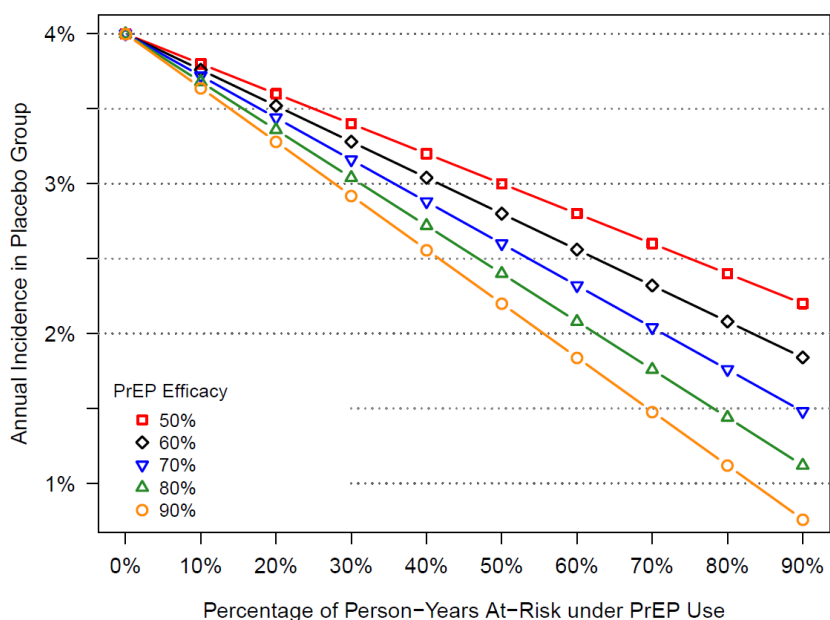


Figure 4-5 Annual HIV-1 incidence in the control group assuming 4% annual HIV-1 incidence in the hypothetical scenario of no PrEP use, under different levels of PrEP use and levels of PrEP efficacy

Higher than expected use of PrEP would be reflected in lower than expected annual incidence rates, as shown in Figure 4-5. As shown in Figure 4-2, the trial would still provide enough statistical information to be powered to detect highly relevant prevention efficacy effect sizes if annual incidence rates are lower than we have estimated here due to higher than expected use of PrEP.

4.7 Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group

Table 4-4 reports power calculations for comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. The calculations assume the scenarios for true values of PE10 and PE30 indicated in the first two columns of the table. The results show that the study is well-powered to detect large differences, for example, with about 87% power to discriminate 30% vs. 80% PE and 40% vs. 85% PE, but may miss moderate differences (e.g., 34% power to discriminate 30% vs. 60% PE). In contrast, the study has high power to correctly select the best mAb dose group given moderate efficacy differences. Specifically, if the true PE30 is moderately greater than the true PE10, then there is high probability that the estimated PE30 would be greater than the estimated PE10, such that the 30 mg/kg mAb dose group would be selected.

Table 4-4 Statistical power for comparing the 10 versus 30 mg/kg mAb groups: Power to correctly rank-and-select the best mAb group and power to detect superiority of the 30 mg/kg mAb group over the 10 mg/kg mAb group in a head-to-head comparison

PE10	PE30	Power to Rank-and-Select Best mAb Dose Group [§]	Power to Detect PE10 Different from PE30 [#]
20%	60%	88.3	58.3
30%	60%	86.7	39.5
40%	60%	81.7	21.6
20%	70%	97.2	83.7
30%	70%	96.8	69.4
30%	80%	99.8	91.5
40%	85%	>99.9	90.8
50%	85%	99.7	77.0

[§] Probability that the mAb dose group that is truly better (the 30 mg/kg dose group in the scenarios considered in the table) is correctly selected based on the point estimate for PE30 exceeding that for PE10. Specifically, correct selection entails that the estimated PE30 is greater than the estimated PE10 and PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

[#] Cumulative hazard-based Wald tests comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. Rejection of the null hypothesis requires that PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

4.8 Sample size calculations for safety

We consider the statistical power of Fisher's exact test to detect a higher rate of SAEs in a mAb group (Group 1 or 2 with $n = 900$ participants) versus the control group (Group 3 with $n = 900$). Based on HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE. The tests use a 2-sided α -level of 0.05. This level does not correct for the 4 comparisons; however, this is appropriate because it is desirable to maximize power to detect a safety problem. For the safety calculations, we assume no missing data as almost all participants will have some follow-up data for safety.

To describe the precision of the study to characterize differences in SAE rates between groups, Table 4-5 shows 2-sided 95% CIs for different levels of observed differences (mAb group-control) of event rates between a mAb group of size $n_1 = 900$ (or the combined mAb groups $n_2 = 1800$) and a control group of size $n_0 = 900$. For example, an observed rate difference of 6% between the combined mAb groups and control group will lie between 3.5% and 8.7% with 95% confidence, when the observed event rate in the control group is 4%.

Table 4-5 Two-sided 95% CIs for different observed event rate differences of safety endpoints between the mAb recipient and control groups*

Observed event rate in controls (n0 = 900)	Observed event rate in a single mAb group (n1 = 900)	Observed event rate in combined mAb groups (n2 = 1800)	Rate difference (mAb group – control)	95 % CI (n1 = 900)	95% CI (n2 = 1800)
0/900 = 0%	0/900 = 0%	0/1800 = 0%	0%	(-0.0050, 0.0050)	(-0.0050, 0.0022)
	18/900 = 2%	36/1800 = 2%	2%	(0.0125, 0.0317)	(0.0143, 0.0278)
	36/900 = 4%	72/1800 = 4%	4%	(0.0289, 0.0550)	(0.0317, 0.0503)
	90/900 = 10%	180/1800 = 10%	10%	(0.0817, 0.1217)	(0.0869, 0.1150)
	180/900 = 20%	360/1800 = 20%	20%	(0.1750, 0.2279)	(0.1819, 0.2192)
18/900 = 2%	0/900 = 0%	0/1800 = 0%	-2%	(-0.0317, -0.0125)	(-0.0317, -0.0125)
	16/900 = 2%	36/1800 = 2%	0%	(-0.0136, 0.0136)	(-0.0127, 0.0106)
	32/900 = 4%	72/1800 = 4%	2%	(0.0041, 0.0369)	(0.0060, 0.0327)
	80/900 = 10%	180/1800 = 10%	8%	(0.0592, 0.1030)	(0.0631, 0.0968)
	160/900 = 20%	360/1800 = 20%	18%	(0.1531, 0.2088)	(0.1594, 0.2009)
36/900 = 4%	0/900 = 0%	0/1800 = 0%	-4%	(-0.0550, -0.0289)	(-0.0550, -0.0289)
	18/900 = 2%	36/1800 = 2%	-2 %	(-0.0369, -0.0041)	(-0.0360, -0.0067)
	36/900 = 4%	72/1800 = 4%	0%	(-0.0188, 0.0186)	(-0.0170, 0.0150)
	90/900 = 10%	180/1800 = 10%	6%	(0.0369, 0.0842)	(0.0405, 0.0787)
	180/900 = 20%	360/1800 = 20%	16%	(0.1314, 0.1899)	(0.1372, 0.1826)

*95% CIs are computed using the method of Berger and Boos [115].

Figure 4-6 shows the power to detect an elevated SAE rate as a function of the true rate in the mAb group under consideration.

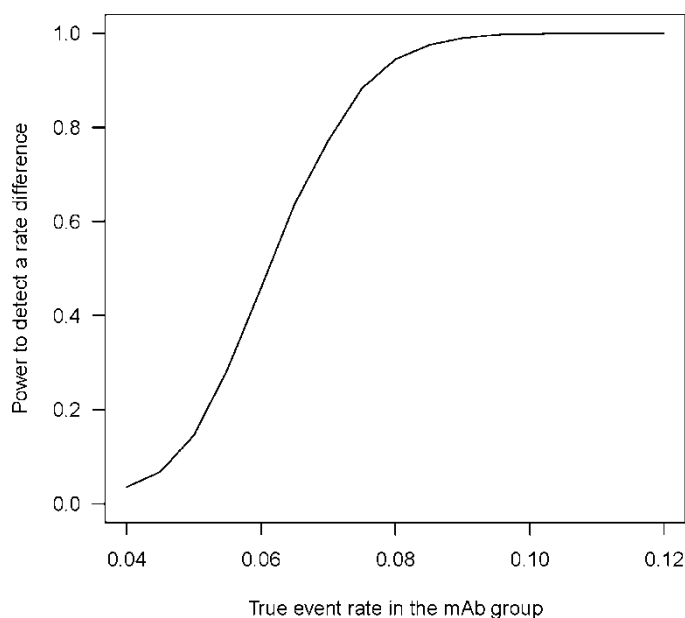


Figure 4-6 Power to detect a greater SAE rate in a mAb group (n = 1800) versus the control group (n = 900) given a 4% SAE rate in the control group (2-sided 0.05-level test)

Figure 4-6 shows that there is 80% power to detect a higher SAE rate in a mAb arm if the true SAE rate is 7.1% and 90% power if the true rate is 7.6%.

4.9 Monitoring of the trial

4.9.1 Role of the Data Safety Monitoring Board (DSMB)

The study DSMB will review unblinded study data at 6-monthly interim analyses to evaluate safety, integrity, and efficacy of the ongoing trial. Following each DSMB meeting, the DSMB reports to the Oversight Committee (OC) a summary of the trial review, which may include recommendations to modify or terminate the trial. The DSMB is guided by a trial monitoring plan, and reviews and approves the monitoring plan before the trial initiates.

Each 6-monthly DSMB report will include a complete analysis of safety data. If a total of $N = 20$ participants reach the Week 12 study visit before the first DSMB report is generated, then a safety report based on these data will be provided to the DSMB as soon as possible and before the first DSMB meeting. The contents of the early report are the same as the contents in the scheduled 6-monthly DSMB reports.

In addition, as soon as 10 grade 2 or higher AEs occur, a report will be generated describing these AEs and will be provided to the DSMB. The DSMB reports will also tabulate occurrence of SAEs, and of AEs judged related to product, accounting for the number of infusions received.

Moreover, as described in Section 1, the safety run-in cohort includes up to 675 enrolled participants, with an enrollment pause, if necessary, after the 675th enrolled participant. Once the 450th enrolled participant (possibly including participants in the safety run-in in sister study HPTN 703/HPTN 081) reaches the Week 24 study visit, a comprehensive safety report is compiled and provided to the DSMB. If the safety data are deemed satisfactory, then enrollment would recommence (or continue).

4.9.1.1 Sequential monitoring for potential harm, non-efficacy, and high efficacy

The trial uses sequential monitoring of the mAb groups versus control to stop early for:

- Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring-adjusted 90% CI lying below 0%]
- Non-efficacy [Establish that PE (pooled over the mAb groups) $< 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
- High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

The sequential monitoring is based on CIs in order that the result of the study that would be reported would convey evidence supporting the conclusion of potential harm, non-efficacy, or high efficacy. Freidlin, Korn, and Gray [116] discuss a rationale for this approach to non-efficacy monitoring. The sequential monitoring for potential harm is based on monitoring-adjusted 1-sided 0.05-level tests (instead of 1-sided 0.025-level tests) for prudence to protect the safety of study participants (ie, less precision is required to meet a guideline for potential harm than to meet guidelines for non-efficacy or high-efficacy). Once non-efficacy monitoring commences, the potential harm monitoring after each infection ceases, as the non-efficacy monitoring now provides the function of detecting an elevated rate of HIV-1 infection. The non-efficacy monitoring is

supplemented with conditional power calculations that report estimates of the probability of rejecting the null hypothesis of zero PE under different assumptions about the estimated PE if the trial were to continue to the end. The sequential monitoring plan is summarized in Table 4-6 and Figure 4-7.

Table 4-6 Summary of sequential monitoring of PE

Monitoring Type	Hypotheses	Testing Approach	Size of Test	Stopping Boundary	Timing of Interim Analyses
Potential Harm	H0: PE $\geq$ 0% vs H1: PE < 0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the mAb	Specified in the monitoring plan	Near-constant 1-sided p-value cut-off controlling the FWER at $\alpha = 0.05^*$	After every infection from 20 th total until first non-efficacy analysis
Non-Efficacy	H0: PE $\geq$ 40% vs H1: PE < 40%	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI below 40% supplemented with conditional power (specified in the monitoring plan)	6-monthly starting based on an event-driven trigger specified in the monitoring plan
High Efficacy	H0: PE $\leq$ 70% vs H1: PE > 70%	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI above 70%	6-monthly starting at the same time as for non-efficacy

* Equivalently, a monitoring-adjusted 2-sided 90% CI based on inversion of the test statistic lies below 0%. The 1-sided p-value significance threshold stopping boundaries after each infection event are specified in the study monitoring plan.

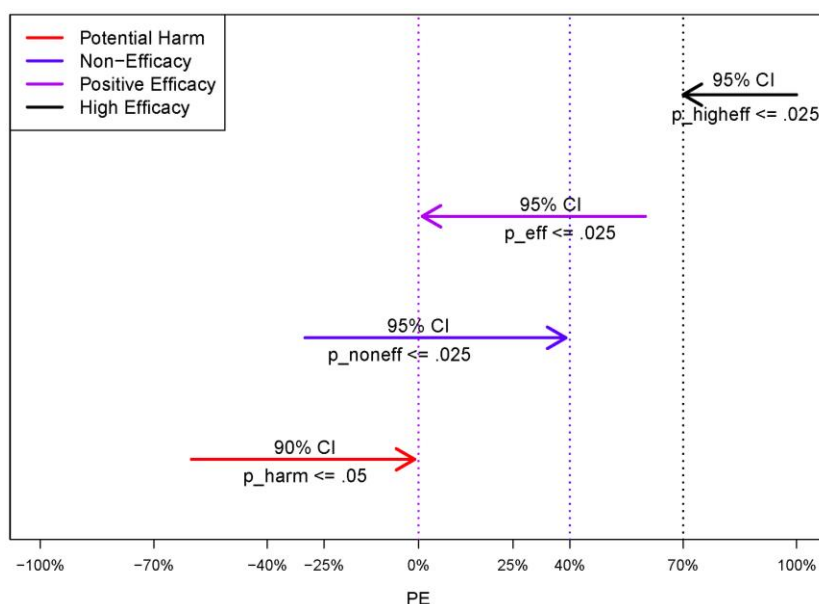


Figure 4-7 Stopping boundaries for the sequential monitoring based on 2-sided CIs

Details of the sequential monitoring plan will be provided in a separate trial monitoring plan. The sequential monitoring is closely related to what was done for the HVTN 505 HIV-1 vaccine efficacy trial [117] (background discussion in [71]).

4.9.2 Feasibility check and guideline for continuing enrollment as planned

In addition to the sequential monitoring of PE, feasibility monitoring is done for the first 120 enrolled participants. This feasibility monitoring is based on the first four 8-week intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of

participants attend clinical visits and receive the infusions per the protocol. The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) supplemented by data on visit attendance, which corresponds to adherence to receipt of infusions. Additional details will be provided in the trial monitoring plan.

The feasibility monitoring based on the first 120 enrolled participants will use the following guideline for continuing enrollment as planned: continued participation by the Week 32 visit pooled over the 3 groups is greater than 80%.

If the blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is warranted.

4.9.3 Monitoring for futility to assess PE

Define the Target Number of Infections to be the number of primary endpoint diagnosed HIV-1 infections after Week 0 and by the Week 80 visit such that the trial has approximately 70% power to reject $H_0: PE \leq 0\%$ if $PE = 60\%$ in the primary analysis. This number is 29, calculated based on the simulated trials described above. Define the Time to the Target Number of Infections (TTNI) to be the number of months from the time of the first enrolled participant until the 29th HIV-1 primary endpoint infection. The objective of monitoring for futility to assess PE is to provide to the DSMB periodic projections of the estimated distribution of the TTNI. If the probability of reaching the TTNI within a specified time frame is too low, then a guideline would be met for recommending completing the trial based on the inability to answer the primary PE question in a timely manner.

The projections of the TTNI will be provided to the DSMB at each 6-monthly DSMB meeting starting at the meeting taking place at least 6 months after the first volunteer is enrolled. This calculation will use the observed recruitment, HIV-1 incidence, and retention rates. The sample size calculations assume 32 months of enrollment and 80 weeks (= 18.46 months) of total follow-up per participant for monitoring for primary HIV-1 infection endpoints, constituting 32 + 18.46 months = 50.46 months. If the projected TTNI reliably exceeds 50.46 months after trial opening, then the DSMB should consider maneuvers to reduce this waiting time. In particular, if continued recruitment could reduce the projected TTNI by more than 3 months, sites (or selected sites with relatively high recruitment rates) would be expected to extend recruitment for up to 6 months. If the projected TTNI reliably exceeds 60 months (5 years) after appropriate attempted remediation, then the OC will consider recommending termination of the trial. In the event that the trial is terminated, then at that time the final analysis would be performed.

Calculation of the projected TTNI at an interim analysis

The method for projecting the TTNI is based on the following approach to simulating efficacy trials. A similar process was used for HVTN 505. The trial is modeled as a combination of three processes — enrollment, dropout, and HIV-1 infection — and a large number of trials is simulated. The three processes are assumed independent and their distributions are taken to be Poisson, exponential, and exponential, respectively. Data are generated at the level of the individual participant, such that for each participant we obtain an enrollment time, an (underlying true) infection time, and a dropout time. Only the minimum of the infection and dropout times is observable, and the average value for

this minimum is beyond the duration of the trial, such that neither event will be observed for most participants. The parameters for the enrollment, infection, and dropout processes are chosen to match our pre-trial assumptions regarding these rates:

- Enrollment rate: 9.72 participants per week in weeks 1-13; 19.43 participants per week in weeks 14-130
- Dropout rate: 0.10 dropouts/person-year
- Infection rate: 0.03 infections/person-year

The first step in simulating each trial is to enroll a certain number of participants per week according to a random draw from a Poisson distribution with rate parameter as listed above. Enrollment continues week-by-week until a total of 2700 participants is reached. Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. Following enrollment, the infection and dropout times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider dropout events to have occurred at the dropout time (in days) that was generated (assuming it was less than the infection time). For participants who become HIV-1 infected, we record their time of diagnosis as the time of the first study visit following the true infection time. It is this time of diagnosis that we observe for infected participants.

Once all participants have had their enrollment and infection/dropout times generated and (if necessary) infection diagnosis time determined, we can then obtain the TTNI for the simulated trial. For participants with HIV-1 infection diagnosis, we add their enrollment and infection diagnosis times together to obtain diagnosis times that are relative to the beginning of the study (in calendar time) rather than in relation to their own enrollment times. Finally, we order these participants by these new infection diagnosis times, from smallest to largest, and identify the 29th one from the beginning. The TTNI is this 29th infection diagnosis time after Week 0 by the Week 80 visit.

A modification of the above procedure for simulating the efficacy trial is used for predicting the TTNI at a given interim analysis. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on pre-trial assumptions. In particular:

- Enrollment rate: Estimated based on the rate observed thus far in the study
- Dropout rate: Estimated based on the rate observed thus far in the study
- Infection rate: Estimated based on a posterior distribution for the infection rate formed by combining the observed data with our prior belief about the infection rate based on the pre-trial assumptions

A new value for the infection rate is sampled from the posterior distribution for each simulated trial. The rationale for this approach is to help stabilize the infection rate early in the trial, when insufficient time will have passed to accrue many infections. If we were to rely solely on the observed infections, we might by chance obtain a very low rate, which would lead to an unrealistic prediction of the TTNI. The effect of the prior is

highest early in the trial, when we have the least data, and is gradually reduced as more trial data accumulate. By the year 2 interim analysis, the prior has little effect. We use a gamma distribution prior (which is conjugate to the exponential used for the infection rate), with parameters chosen so that the prior mean matches the pre-trial assumption for the infection rate and with information content approximately equivalent to what is expected in the first 12 months of the study.

At a given interim analysis, the TTNI is estimated based on simulating 100,000 trials using the above procedure, each of which yields a predicted TTNI. The projected TTNI is the median predicted TTNI over the 100,000 trials. As noted earlier, the guideline for declaring futility to assess PE is that the projected TTNI lies reliably above 5 years. Our translation of this into practice is that we require that at least 75% of the 100,000 predicted TTNI values be greater than 5 years (ie, the probability that the true TTNI is greater than 5 years is at least 0.75).

The trial monitoring plan will include evaluation of the operating characteristics of the TTNI projection method.

Performance standards for quality of trial conduct

The protocol team and study investigators will have performance standards regarding the quality of trial conduct in addition to the HIV-1 infection diagnosis rate. In addition to projections of the distribution of the TTNI, at each interim analysis the DSMB is provided treatment-pooled plots of enrollment over calendar time. Kaplan-Meier estimates of treatment-pooled cumulative incidences of dropout, discontinuation of mAb infusions, and HIV-1 infection is also provided, together with Kaplan-Meier estimates of the cumulative incidence of “discontinued participation” that can occur due to dropout or to withdrawal from receipt of infusions. In addition, tables will be provided summarizing expected versus observed 4-weekly visit attendance rates and rates of received infusions among participants attending visits. All of these results will be provided overall and by study site. The DSMB and the protocol team leadership will monitor whether the trial is achieving at least minimally acceptable levels regarding key performance standards.

Feasibility check

When the data are available for the feasibility check, a feasibility check report will be generated and provided to protocol team leadership and the DSMB. As stated above in Section 4.9.2, the feasibility monitoring based on the first 120 enrolled participants will use the following guideline for continuing enrollment as planned: continued participation by the Week 32 visit pooled over the 3 groups is greater than 80%, where continued participation means not dropping out and not permanently discontinuing infusions by the Week 32 visit. Details about the contents of the feasibility check report are provided in the study monitoring plan.

4.10 Assessment of ARV drug use

Studies by the HPTN Laboratory Center have documented that off-study ARV drug use may not be disclosed to study staff [118-121]. Use of a high-throughput multi-drug assay will allow assessment of both use of TFV/FTC for PrEP (either off-study or provided in the study), as well as use of other ARVs that may impact study outcomes (eg, by lowering HIV incidence with a loss of study power). Because there are relatively few

data describing patterns of ARV use in the relevant study populations and regions, and because patterns of ARV use among HIV-uninfected individuals may be regional [121] and are likely to change over time, it is difficult to predict the prevalence or pattern of ARV drug use in the study.

The ARV assay described in Section 9.6 will provide information on the prevalence of ARV drug use in the study population, as well as the type of ARVs used. For individuals who acquire HIV infection during the study, samples may be tested from the first HIV-positive visit and selected prior study visits to assess ARV use. Samples from individuals who are not infected may be tested for comparison, to explore a potential impact of ARV use on PE of the study product. Data obtained using the ARV assay will also be compared to data collected from self-reported ARV use (eg, for PrEP, PEP, recreational use). In addition to reporting ARV drug use to the DSMB and the OC, the protocol team leadership will see results summarizing ARV drug use among participants (treatment pooled data only).

A detailed plan has been developed to prospectively monitor ARV assay data in HIV-1 negative study participants, which is detailed in the study monitoring plan.

4.11 Randomization

The randomization sequence will be obtained by computer-generated random numbers and provided to each CRS through a Web-based randomization system. The randomization will be done in blocks to ensure balance across arms. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the SSP).

4.12 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know this information in order to ensure proper trial conduct. Any discussion of study product assignment between pharmacy staff and any other CRS staff is prohibited.

When a participant leaves the trial prior to study completion, the participant will be told he or she must wait until all participants are unblinded to learn his or her treatment assignment.

Emergency unblinding decisions will be made by the site investigator. If time permits, the HVTN 704/HPTN 085 PSRT should be consulted before emergency unblinding occurs.

4.13 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many infusions they received. In the rare instance that a participant receives the wrong treatment at a specific infusion visit, the Statistical Analysis Plan will address how to analyze the participant's safety data. Analyses are modified intent-to-treat (MITT) in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected.

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

4.13.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, efficacy, and markers of mAb characteristics for primary- and secondary-objective analyses.

4.13.2 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

4.13.3 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first infusion, all participants will have received at least 1 infusion and therefore will provide some safety data.

4.13.3.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

4.13.3.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

4.13.3.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section 10.2.2) will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

4.13.3.4 Reasons for infusion discontinuation and early study termination

The number and percentage of participants who discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

4.13.4 Efficacy analysis

4.13.4.1 General approach

For the statistical analysis of prevention efficacy, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Given that all or almost all participants will receive the first infusion, the analyses are MITT, where all participants HIV-1 negative at entry receiving the initial infusion are included in the analysis, participants are analyzed according to their randomized treatment assignment, and participants retrospectively determined to be HIV-1 infected at entry based on treatment blinded procedures are excluded from the analysis. Additional analyses may be performed, limited to participants who received most or all infusions per protocol.

Cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms will be estimated by a transformation of Nelson-Aalen estimators [122] for the respective cumulative hazard functions of HIV-1 infection. PE parameters will be estimated by one minus the ratio (mAb/control group) of these cumulative incidence estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported. These procedures will be used to test the hypotheses listed in Section 4.2.

As a supportive analysis for the hypotheses listed in Section 4.2, targeted maximum likelihood estimation (tMLE) will be used to estimate cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms [123,124]. The Statistical Analysis Plan will describe the details of implementation of the tMLE estimators in an automated and objective fashion. PE parameters will be estimated by 1

minus the ratio (mAb group/control) of these tMLE estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of HIV-1 infection over time, complementary secondary analyses will assess hazard-ratio based prevention efficacy using Cox proportional hazards models with score tests stratified by VRC01 dose group for testing whether prevention efficacy differs from zero. This analysis uses as the failure time the time from the most recent infusion to the estimated date of HIV infection, entered in the Cox model as a time-dependent covariate. This analysis can have increased power to detect prevention efficacy compared to the primary analysis of the cumulative incidence based parameter PE, if instantaneous prevention efficacy is higher when VRC01 concentrations are lower. Goodness-of-fit diagnostics will be applied to assess veracity of the proportional hazards assumption. The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity of the primary analysis does not depend on the proportional hazards assumption. The Cox model will also be used for a secondary analysis of PE in subgroups defined by the level of cumulative infusion adherence over time included in the model as a time-varying covariate.

Sensitivity analyses of the primary analysis will test $H_0: PE = 0\%$ with a log-rank test and with a Gehan-Wilcoxon test stratified by VRC01 dose group. To explore potential time-variations in prevention efficacy, instantaneous prevention efficacy over time defined based on the instantaneous hazard ratio (VRC01 vs. placebo) will be estimated with pointwise and simultaneous confidence bands using nonparametric kernel smoothing [125].

4.13.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety or efficacy endpoint assessments.

4.13.6 Specific approach for assessing PE, PE10, PE30

Primary objective 2 is addressed based on comparing cumulative HIV-1 incidence between the group of participants assigned to receive the VRC01 mAb (at either dose pooling over the two doses) and the group of participants assigned to the control group, and secondarily between each individual mAb dose group and the control group. For each prevention efficacy parameter PE, PE10 and PE30, point and 2-sided 95% CI estimates will be reported, along with the 2-sided p-values for testing the respective null hypotheses (with 2-sided $p = 0.05$ the threshold for a significant effect). Unadjusted and Holm-Bonferroni p-values will be reported for testing of the secondary endpoint efficacy parameters PE10 and PE30.

4.13.7 Assessment of individual-level markers of VRC01 mAb that correlate with protection against HIV infections (Secondary objective 1)

Secondary objective 1 is addressed based on the measurement of VRC01 mAb markers over time in mAb group breakthrough HIV-1–infected cases and in a random sample of HIV-1–uninfected mAb group participants (marker subset), integrated with the genotypic and phenotypic sieve analysis of breakthrough HIV-1 viruses accounting for knowledge

of the VRC01 antibody footprint. The main analyses of the secondary objective 1 pool over the two mAb doses to maximize statistical power.

The design and results requirements for successful identification of correlates of protection in secondary objective 1 are:

1. Sufficient sample size to observe enough participants diagnosed with incident HIV-1 infection during the primary follow-up period of 80 weeks postenrollment in the mAb arms
2. A result of significant beneficial overall mAb PE > 0%
3. Sufficiently frequent HIV-1 testing schedule and accurate HIV-1 diagnostics
4. Wide variability in the concentration and effector functions of the mAb over time and/or individuals, and the ability to measure these characteristics such that their timing relative to the timing of HIV-1 acquisition is estimated with adequately low measurement error
5. mAb marker sampling design that allows sufficiently accurate PK modeling of mAb characteristics over time

Note that the serum concentration mAb markers (secondary endpoints 2) are defined without reference to a particular HIV-1 Env sequence. The effector function markers (also secondary endpoints 2) are relative to specific HIV-1 Envs or panels of Envs, and thus may be linked to immunogenicity endpoints (and the antigen reagents for those endpoints) that would be used in future trials of candidate HIV-1 vaccines. Correlates of protection analyses directly assess how mAb PE depends on markers.

4.13.7.1 Sampling of mAb markers

Characteristics of the mAb or immune responses to the mAb are measured in participants assigned to the mAb treatment groups, and in a small number of participants assigned to the control group. The sampling design determining the set of participants for measuring the markers will be finalized after the primary analysis results. This sampling design will include measuring the markers in all mAb group primary endpoint cases with a minimal number of samples available prior to diagnosis of HIV-1 infection, and on a random sample of participants from each mAb group who complete follow-up to the Week 80 visit HIV-1 negative (mAb group control participants). The random sample of HIV-1 uninfected controls is chosen to create a common control:case ratio across participant strata defined by factors such as dose group, infusion adherence, and calendar period of enrollment. For participants assigned to the control group, a smaller number of cases and HIV-1 negative controls will be sampled for measurement of markers. The timing of marker measurements is as follows:

- mAb group and control group cases: visits every 4 weeks up until the time of HIV-1 diagnosis and Day 61 (5 days post second infusion) if before diagnosis, plus the first positive visit and additional time-points post HIV-1 infection
- mAb group and control group marker subset controls: visits every 4 weeks through Week 92 plus Day 61

The Day 5 post-second infusion visit is included because it occurs shortly after the end of the distributive phase of the mAb, which together with the samples drawn just before infusions (Week 0, 8, ..., 72), the samples drawn 4 weeks post-infusions (Week 4, 12, ..., 76), and the Week 80, 84, 88, 92 samples 8–20 weeks post last infusion constitute the basis for modeling marker curves over time.

4.13.7.2 Overview of the analysis of a mAb marker as a correlate of protection

A correlates of protection statistical analysis plan will be finalized not using any information on case-control status of participants; this plan will contain details of the statistical analysis. We provide a brief summary here. For a given mAb recipient, let $S(t)$ be a marker characteristic at time t postenrollment in days, for example the time-concentration curve. The entire curve $S(t)$ cannot be known exactly given that the marker is measured at a grid of time-points. A PK model will be used to express $S(t)$ as a function of the measured marker readouts and error terms. One approach to the correlates of protection analysis will estimate the “prevention efficacy curve” $PE(S(t) = s)$ defined as

$$PE(S(t) = s) = [1 - (\text{hazard-mAb}(S(t) = s)) / (\text{hazard-control}(S(t) = s))] \times 100\%$$

where $\text{hazard-mAb}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to either mAb group with $S(t) = s$ and $\text{hazard-control}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to the control group who would have had $S(t) = s$ had s/he been assigned to the same mAb group (thus $S(t)$ is a counterfactual random variable for control recipients). Similar parameters are used for assessing time-dependent correlates of protection in vaccine efficacy trials. A time-dependent parameter is used because interest centers on understanding how the current value of a mAb marker associates with the level of instantaneous PE given exposure with an HIV-1 virus at that time. The statistical analysis plan will describe the methods used to estimate $PE(s)$ over the range of values s of a mAb marker characteristic. In addition to estimation, hypothesis testing will be performed to assess whether a mAb marker modifies PE, ie, testing

$$H_0: PE(S(t) = s) = PE \text{ versus } H_1: PE(S(t) = s) \text{ varies in } s. \quad (1)$$

Rejecting H_0 in favor of H_1 supports the role of the marker in protection. The correlates of protection analysis pools over the two mAb groups, for the purpose of improving power both through a larger sample size and through greater inter-individual variability of the mAb markers. Given that the exact dates of infusions have a major impact on mAb markers $S(t)$ such as concentration over time (eg, notice the profound influence of missed infusions on $S(t)$ in Figure 2-9, the analysis accounts for the exact dates of infusions that are expected to show considerable heterogeneity across trial participants.

4.13.7.3 A time-window approach to assessing mAb correlates of protection

To explain the concept of this approach, first suppose all participants received all scheduled infusions and rigidly followed the visit schedule. Then this approach compares HIV-1 incidence during the first 4 weeks of the infusion intervals (ie, weeks 1-4, 9-12, 17-20, ..., 73-76) to HIV-1 incidence during the second 4 weeks of the infusion intervals (ie, weeks 5-8, 13-16, 21-24, ..., 77-80), aggregating over the ten 8-week infusion intervals. Because the mAb has much higher concentration during the first halves of the infusion intervals compared to the second halves (eg, demonstrated in Figure 2-9), detection of higher HIV-1 incidence in the second halves of visit windows

would imply that higher concentrations are associated with a lower rate of HIV-1 infection.

However, because of missed infusions and the heterogeneity among participants of infusion dates (which is allowable as specified by broad visit windows), a better approach accounts for the set of exact infusion dates of each participant. As such, our approach to implementing the time-window approach compares the mean time between the last infusion and infection for VRC01 group cases, with the mean of the participant-specific weighted average time between infusions of VRC01 group control participants, where the weights allow for changing HIV-1 incidence over time. The analysis stratifies by the 10 mg/kg and 30 mg/kg dose groups and aggregates estimates over these two dose groups. In addition, an important element of the analysis uses predictions of the HIV-1 infection times for all VRC01 group cases. Models for these predictions are built using information on HIV-1 diagnostic tests, intra-host diversity of HIV-1 sequences, HIV-1 viral loads, and perhaps other factors. Initial research to build predictors of HIV-1 infection time based on HIV-1 sequence information has been conducted using validation data sets of acutely HIV-1 infected individuals [126].

A related approach to assessing correlates of protection integrates a pharmacokinetic model of the serum concentration of VRC01 over time, comparing the mean VRC01 concentration at the time of HIV infection for VRC01 group cases with the mean of participant-specific weighted average VRC01 concentrations over follow-up time. The participant-specific average VRC01 concentration over follow-up time is intended to reflect the expected concentration at the time of a random HIV exposure, with weighting used as above to allow for changing HIV-1 incidence over time. Details of these statistical methods will be provided in the statistical analysis plan.

4.13.7.4 mAb markers

For effector function markers measured based on a sample from a mAb recipient, the markers are measured to each of a panel of HIV-1 Envelope proteins. The most relevant HIV-1 Env panel represents the VRC01 antibody footprint diversity of viruses exposing trial participants. For example, relevant for the study population of North/South American MSM + TG, Figure 4-8 shows a logo plot of the VRC01 antibody footprint motifs comprising 35 amino acid sites [127,128] based on 276 subtype B US and South American sequences deposited in the Los Alamos National Laboratory (LANL) sequence database between 2006 and 2014. There are 272 unique mAb footprints.

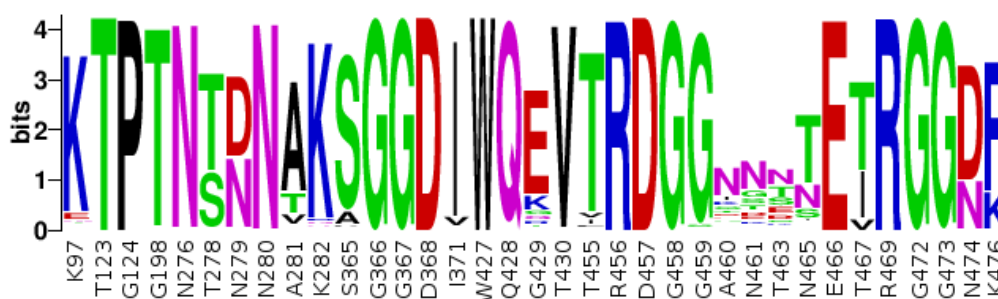


Figure 4-8 Logo plot of the VRC01 antibody footprints that occur in 276 subtype B US and South American sequences deposited in the LANL sequence database between 2006 and 2014

During the conduct of the trial the research team will determine a minimal set of Envs constituting a panel capturing most of the VRC01 mAb footprint diversity of exposing viruses. One effector function marker of interest for assessing as a correlate of protection is the weighted area under the magnitude-breadth neutralization curve of the mAb footprint Env panel, where the weighting is by the estimated prevalence of mAb footprints in HIV-1s circulating at the trial sites during the trial.

For mAb group participants with a primary study endpoint (breakthrough HIV-1 infection during the first 80 weeks), an important marker is the level at which his/her pre-infection sample at the time of HIV-1 acquisition neutralizes his/her particular breakthrough virus. (This analysis requires modeling the marker at the time of HIV-1 acquisition based on the available grid of marker measurements.) A result where sera from infected participants generally fail to neutralize their founding viruses would support neutralization as a correlate of protection. This analysis is repeated for other effector functions as a way to discriminate which effector functions are or are not correlates of protection, and to rank the effector functions by their contribution to explaining the level of protection.

4.13.7.5 Statistical power for assessing a mAb marker as a correlate of protection

The marker $S(t)$ must vary within mAb recipients over time and/or among mAb recipients in order to detect a correlate of protection, with more variability in one or both components providing greater statistical power to detect a correlate of protection via testing the null hypothesis of equation/panel (1) above. In essence, to detect correlates of protection it is necessary that a large fraction of person-years at risk are in high protection zones and a large fraction of person-years at risk are in low protection zones. (A “high protection zone” is a period of time during which a mAb recipient has high levels of a marker and high levels of efficacy.) Data from VRC 601, VRC 602, and HVTN 104 show wide variability in the mAb concentration over time, and more limited variability among mAb recipients. HVTN 104 will provide more data on these two aspects of marker variability. The limited among-mAb recipient variability motivates the study design that randomly assigns participants to 2 different mAb doses in order to create inter-individual variability.

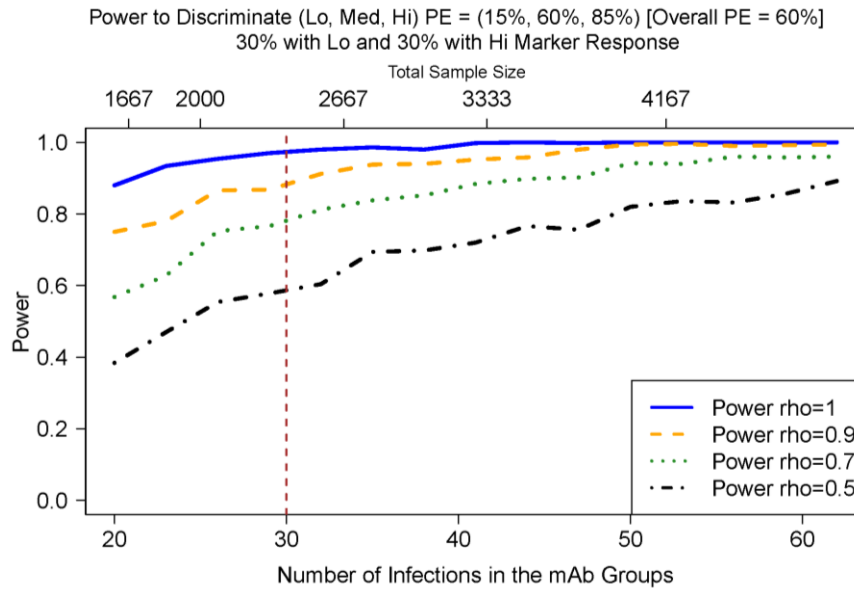
Achieving adequate power to detect correlates of protection requires that the HIV-1 diagnostic testing is more frequent than the infusion schedule. This is why diagnostic visits every 4 weeks are advantageous given infusions every 8 weeks, and procedures may be determined and applied to test for HIV-1 infection more frequently than every 4 weeks. The data from all of the employed diagnostic testing kits is incorporated into the modeling of $S(t)$ and of HIV-1 infection times, and is integrated into the modeling of $S(t)$ and into the statistical analysis for estimation and testing of $PE(S(t) = s)$. Lastly, achieving adequate power to detect correlates of protection requires studying markers that can be measured with a high ratio of potentially protection relevant variability versus protection irrelevant variability, where the latter variability could stem from technical measurement error of the assay or to error in estimation of the timing of infection. Because of this fact the trial design relies on parallel assay studies to qualify marker variables for the analysis and relies on development and characterization of models for $S(t)$ over continuous time t .

We provide one power calculation for assessing a trichotomous marker $S(t)$, the concentration of the mAb at time t post enrolment, as a correlate of protection, which divides the pooled mAb group at a given time t by two thresholds of marker response

[$S(t) = 0$ indicates Low, $S(t) = 1$ indicates Medium, and $S(t) = 2$ indicates High for some pre-set definitions of Low, Medium, High]. Thus at any given time t after entry, $S(t)$ divides the pooled mAb group into three subgroups. In our illustration we take “0” to be a VRC01 serum concentration ≤ 50 mcg/mL, “2” to be a VRC01 serum concentration > 10 mcg/mL, and “1” to be an intermediate serum concentration.

Based on Figure 2-4, we conduct a power calculation indexed by the percentage of person-years at-risk of mAb recipients that are in the (Low, Medium, High) zones, and indexed by the level of PE within each of these zones. As indicated in the figure, we expect that about (50%, 40%, and 10%) of the PYRs at risk in the 10 mg/kg mAb group are in the (Low, Medium, and High) regions whereas about (10%, 40%, and 50%) of the PYRs at risk in the 30 mg/kg mAb group are in the (Low, Medium, and High) regions. We consider power calculations pooling data across both mAb groups, assuming 30 mAb HIV-1–infected cases with data and 150 mAb group HIV-1–uninfected controls with data, assuming the design alternatives $PE_{10} = PE_{30} = 60\%$ approximating the numbers displayed in Table 4-3. The detailed mathematical assumptions of these power calculations will be provided in the statistical analysis plan.

Figure 4-9 shows power curves for the scenario that (30%, 40%, 30%) of PYRs at risk are in the (Low, Medium, High) zones (which we approximately expect to occur based on Figure 2-4) and $PE_{10} = PE_{30} = (15\%, 60\%, 85\%)$ in these zones. The power curves also account for noise in the measurement of $S(t)$ via a parameter ρ that equals the proportion of the inter-individual marker variability that is potentially protection relevant. The results show that the noise level majorly affects power, underscoring that only assays meeting qualification criteria will be studied as correlates. The parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values of $S(t)$ are needed. For the scenario that this extra variability reduces ρ to 0.7, there is about 70% power to detect a correlate of protection (with effect size 15%, 60%, 85% efficacy) at the selected trial sample size. Note that the parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values $S(t)$ are needed. A more extensive set of power calculations will be conducted based on HVTN 104 study data.



2-phase logistic regression; 2-sided alpha = 0.05; controls:cases = 5:1

Figure 4-9 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE=15%, 60%, 85%, respectively, for a marker with assay noise parameter $\rho = 1$ (perfect marker), 0.9, 0.7, and 0.5 and percentages of person-years at risk in the (Low, Medium, High) marker regions set at (30%, 40%, 30%). The calculations at 2700 total participants assume 30 mAb group HIV-1–infected cases and 150 mAb group HIV-1–uninfected controls with data on $S(t)$ and pool over both mAb groups. The dashed vertical line represents the sample size of the study.

Figure 4-10 shows the same power analysis as Figure 4-9, fixing $\rho = 0.9$ (indicating a qualifying assay) and varying the percentage of PYRs at risk that are in the (Low, Medium, High) zones. The results show that power increases sharply with the percentage of mAb recipients that are in the Low and High regions, demonstrating the principle that variability in the marker is a strong determinant of power to detect a correlate of protection. For example, the figure shows that the trial has 80% power for the PE = 15%, 60%, 85% effect size if 25%, 50%, 25% of PYRs at risk are in the (Low, Medium, High) zones.

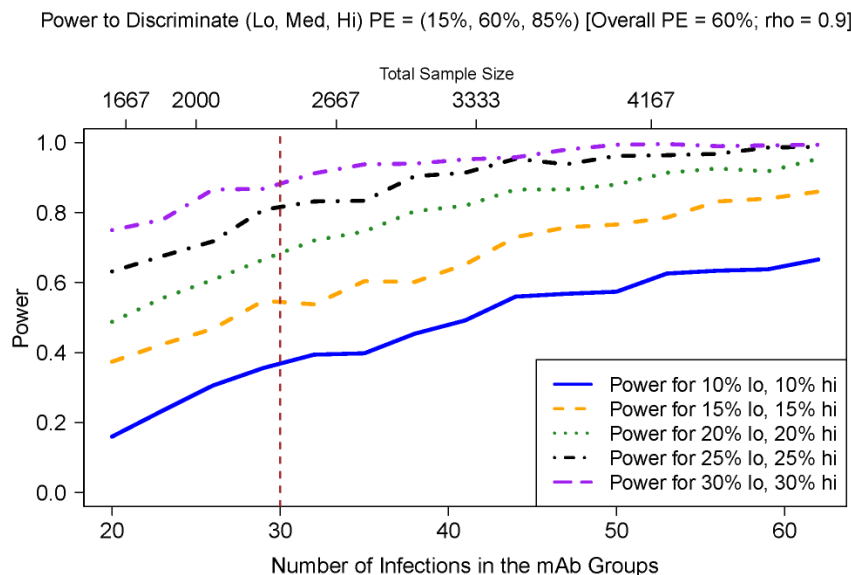


Figure 4-10 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE = 15%, 60%, 85%, respectively, for a marker with assay noise parameter $\rho = 0.9$ and percentages of person-years at risk in the Low and High marker regions varied from 10%, 15%, 20%, 25%, 30%. The calculations at 2700 total participants assume 30 mAb group HIV-1-infected cases and 150 mAb group HIV-1-uninfected controls with data on $S(t)$ and pool over both mAb groups.

4.13.7.6 Genotypic and phenotypic sieve analysis

Genotypic sieve analysis analyzes sequences of breakthrough HIV-1 infecting viruses from the earliest available postinfection sample and seeks to identify amino acid “signatures” that differentiate breakthrough sequences in the mAb groups versus the control group, in terms of differential PE against HIV-1s according to some genotypic characteristics. For example, the genotypic sieve analysis assesses differential PE against different genotypes of HIV-1 with genotype defined by:

- Number of mismatches to the VRC01 mAb footprint of the subtype B consensus sequence (subtype selected to match the circulating HIV-1s)
- Number of known mAb neutralization escape mutations in the mAb footprint
- Number of known mAb effector function escape mutations in the mAb footprint for non-neutralization effector functions such as ADCC, virion capture, and phagocytosis
- Number of potential N-linked glycosylation (PNG) sites within a given radius of the mAb footprint
- Length of variable loops in proximity to the mAb footprint

To illustrate the utility of genotypic sieve analysis, we consider a hypothetical result that would support that the mAb protects via specific neutralization targeting of the mAb’s epitope. In this illustration, the HIV-1 genotype is defined by four ordered genotypes according to whether there are 0, 1, 2, or >2 neutralization escape mutations in the VRC01 mAb antibody footprint. The hypothetical result would be an estimated PE of 95% against HIV-1s with zero escape mutations and a PE of 0% against HIV-1s with >2

neutralization escape mutations, and intermediate and monotone decreasing level of estimated PE against HIV-1 with one mutation and two mutations, respectively.

A second type of sieve analysis, phenotypic sieve analysis, compares breakthrough viruses between the mAb versus control groups using an immunological assay. Specifically, data from an “effector function checkerboard” is filled out, with the rows representing serum samples from a random sample of mAb recipients HIV-1 uninfected at the time of sampling, and the columns representing HIV-1 Env VRC01 footprint targets created from the breakthrough viruses. The phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to mAb recipient sera between the mAb and control treatment groups. A second version of the phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to the VRC01 mAb between the treatment groups; this latter analysis is simpler, based on a single column of data instead of a matrix, because it does not use mAb recipient sera. For an example of the second type of phenotypic sieve analysis, the TZM-bl neutralization assay could be performed on all control breakthrough HIV-1s versus VRC01 and on all mAb group breakthrough HIV-1s (pooled over the two mAb groups) versus VRC01, and a Wilcoxon rank sum test applied to assess a difference. Reduced TZM-bl neutralization sensitivity of the mAb breakthrough group viruses would support that neutralization had a role in protection and that the TZM-bl assay was able to detect this role, and would support using the TZM-bl assay as a tool for evaluating future candidate HIV-1 vaccines. The HVTN has previously conducted neutralization sieve analysis [129]. Figure 4-11 illustrates a genotypic and phenotypic sieve analysis.

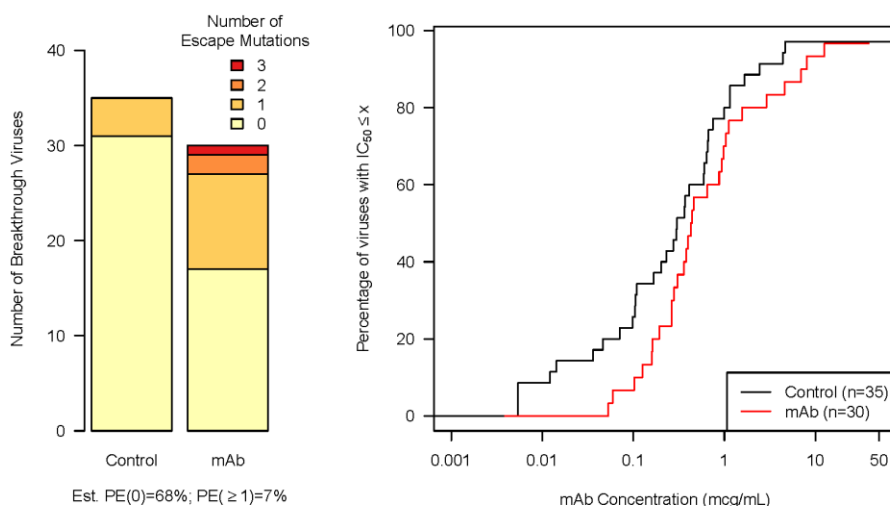


Figure 4-11 Illustration of genotypic (left panel) and phenotypic (right panel) sieve analysis, where the left panel shows the distribution of the number of known neutralization escape mutations in breakthrough control and mAb group HIV-1 sequences, and the right panel shows the percentage of the panel of breakthrough HIV-1s that are neutralized at level 50% (IC₅₀) by the given concentration of the VRC01 mAb.

Another phenotypic sieve analysis focuses on mAb group cases, and measures different effector functions of closest-to-infection participant serum samples or of the VRC01 mAb against the participant-matched breakthrough HIV-1s. The effector functions that tend to have low readouts against participant-matched breakthrough viruses compared to against the panel of control group HIV-1s or compared to an historic panel of HIV-1s are implicated as potential correlates of protection.

In addition, an important sieve analysis will assess PE against HIV-1s that are sensitive to neutralization by VRC01 as measured using the first post-infection sample (sensitive is defined by positive neutralization based on IC_{50} or IC_{80}). This PE parameter measuring prevention efficacy against neutralization sensitive HIV-1s is estimated (with confidence intervals and p-values) in the same way as genotype-specific PE described above. In addition, the same hypothesis testing procedure for detecting differential PE by two HIV-1 genotypes is applied for assessing differential PE by neutralization sensitive versus resistant HIV-1. Moreover, this sieve analysis of sensitive versus resist HIV-1 is also conducted with sensitive/resistant defined by positive/negative response of other assays besides neutralization (eg, ADCC, ADPCP).

4.13.7.7 Illustration of power to detect a phenotypic sieve effect

We conduct power calculations based on TZM-bl neutralization IC_{50} values (in mcg/mL) of VRC07 (a close cousin of VRC01) to approximately 100 viruses representing global HIV-1 diversity (data provided by Mark Louder, Robert Bailer, and John Mascola from the VRC). From the control group we sample 35 HIV-1 infections with IC_{50} from the VRC07 data set, and from the pooled mAb group we sample 30 HIV-1 infections with IC_{50} values bias sampled based on IC_{50} -dependent PE, with $PE(x)$ the probability an infected control recipient would be infected had he (or she) received the mAb with IC_{50} value of x to the exposing virus. Figure 4-12 shows power for comparing the VRC01 IC_{50} distribution of the pooled mAb group HIV-1s versus the control group HIV-1s, based on a two-sample Wilcoxon rank sum test. The effect size indexing a difference between the two groups is equivalently expressed in terms of the $PE(x)$ function (where a horizontal line indicates the null hypothesis of no difference) or in terms of a different cumulative distribution function of the IC_{50} in the two groups. Four correlates effect sizes are considered, ranging from the weakest (Effect Size 1) to the strongest (Effect Size 4). The results show that there is moderate power to detect Effect Size 3 phenotypic sieve effects (second steepest curve in Figure 4-12, power = 0.793).

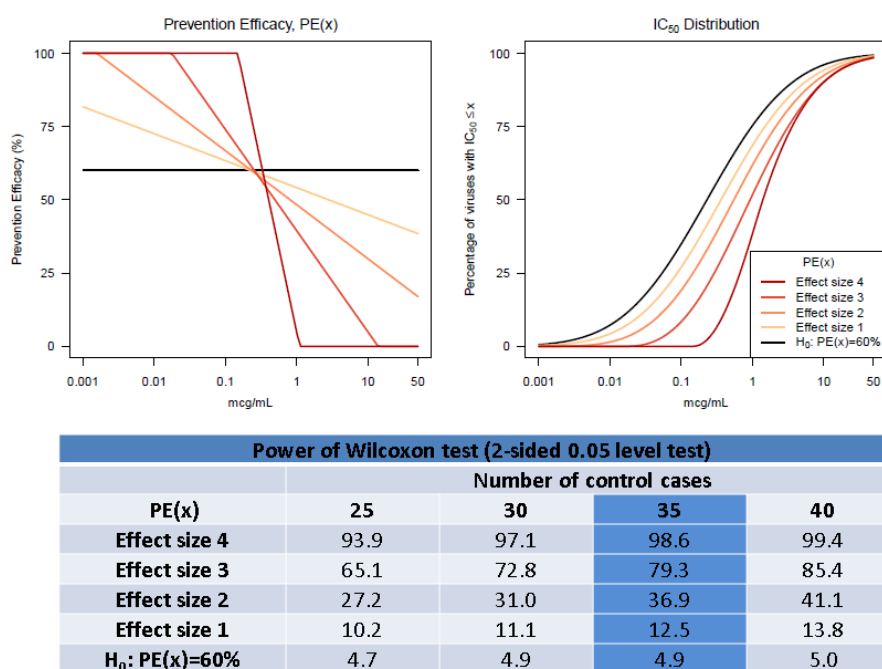


Figure 4-12 Power calculations for comparing IC_{50} distributions between mAb group breakthrough HIV-1s and control group breakthrough HIV-1s, with difference equivalently

expressed in terms of the PE(x) curve or the cumulative IC₅₀ distribution functions, where in the right panel the black/highest curve represents the distribution for the control group breakthrough HIV-1s.

Effect Size 3 is biologically plausible based on the following argument. Under the design alternative of 60% PE we expect a transition between full protection against the most sensitive viruses and zero protection against the most resistant viruses. Table 4-7 shows the percentage of susceptible viruses that are completely blocked by the VRC01 antibody and the percentage of viruses that are completely resistant to the antibody for each of the four specified effect sizes PE(x) in Figure 4-12. For example, for Effect Size 3, the most susceptible 11.6% of viruses are completely blocked (PE = 100%) while the most resistant 2.8% of viruses are completely resistant (PE = 0%) and there is a gradient of protection for the 85.6% of intermediate viruses between the two poles (Table 4-7). The wide range of neutralization (and Fc effector function) sensitivities of HIV-1s suggests that this range of prevention efficacies is plausible. For this effect size there is 79.3% power to detect a phenotypic sieve effect and hence a correlate of protection.

Table 4-7 Percentages of HIV-1s fully susceptible to VRC01 (PE = 100%) and fully resistant to VRC01 (PE = 0%) for the four different effect sizes studied in Figure 4-12

PE(x) Effect Size in Figure 1-16	<i>Susceptible</i> [PE = 100%]	<i>Resistant</i> [PE = 0%]
Effect Size 4	41.9%	23.3%
Effect Size 3	11.6%	2.8%
Effect Size 2	1.0%	<0.1%
Effect Size 1	<0.1%	<0.1%
Null Hypothesis	NA	NA

The sieve analyses will be done including all MITT infected participants, as well as only including mAb group infected participants who received an infusion at the beginning of the 8-weekly interval during which HIV-1 infection was diagnosed.

5 Selection and withdrawal of participants

Participants will be healthy, HIV-uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or serum mAb concentration and efficacy difficult, and some volunteers may be poor candidates for retention.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections 5.1 and 5.2.

5.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 50 years
2. **Access to a participating CRS** and willingness to be followed for the planned duration of the study
3. Ability and willingness to provide **informed consent**
4. **Assessment of understanding:** volunteer demonstrates understanding of this study and completes a questionnaire prior to first infusion with verbal demonstration of understanding of all questionnaire items answered incorrectly
5. **Agrees not to enroll in another study** of an investigational research agent for the duration of the participant's trial participation
6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

7. Willingness to receive **HIV test results**
8. Willingness to **discuss HIV infection risks** and amenable to HIV risk reduction counseling

9. **Persons born Male or identifying as Transgender (TG)** who, in the 6 months prior to randomization, experienced 1 or both of the following HIV risk criteria:

- Condomless anal intercourse with 1 or more male or transgender partner(s)
- Anal intercourse with 2 or more male or transgender partners

Male-to-female and female-to-male TG volunteers are eligible. Receipt of hormonal therapy does not make a TG volunteer ineligible.

Volunteers who have been in a mutually monogamous relationship with an HIV-1 seronegative partner for > 1 year are excluded.

Laboratory Inclusion Values

Hematology

10. **Hemoglobin** (Hgb) ≥ 10.5 g/dL for volunteers who were born female, ≥ 13.0 g/dL for volunteers who were born male
11. **Platelets** $\geq 100,000$ cells/mm³

Chemistry

12. **ALT** < 2.5 times the institutional upper limit of normal and creatinine ≤ 1.25 times the institutional upper limit of normal

Virology

13. **HIV uninfected, as defined in the SSP, within 30 days prior to enrollment**

Urine

14. **Negative, trace, or 1+ (30 g/L for semi-quantitative) urine protein by dipstick**

Reproductive Status

15. **Volunteers capable of becoming pregnant:** negative serum or urine beta human chorionic gonadotropin (β -HCG) pregnancy test performed at the screening visit and prior to infusion on the day of initial infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.
16. **Reproductive status:** A volunteer who is capable of becoming pregnant must agree to consistently use effective contraception (see Appendix B, and SSP) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit.
17. **Volunteers capable of becoming pregnant must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

5.2 Exclusion criteria

General

1. **Investigational research agents** received within 30 days before first infusion
2. **Body mass index (BMI) ≥ 40**
3. **Pregnant or breastfeeding**
4. **Any reactive, indeterminate, or positive HIV test**, even if subsequent testing indicates that the individual is not HIV infected.

Vaccines

5. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 704/HPTN 085 PSRT will determine eligibility on a case-by-case basis.

Immune System

6. **Serious adverse reactions to VRC01 formulation components such as sodium citrate, sodium chloride, and L-arginine hydrochloride**, including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.
7. **Autoimmune disease**, including Type I diabetes mellitus (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require consistent immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate reactogenicity and AE assessments)
8. **Immunodeficiency syndrome**

Clinically significant medical conditions

9. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:
 - Any contraindication to repeated infusions or blood draws, including inability to establish venous access;
 - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period; or
 - A condition or process for which signs or symptoms could be confused with reactions to VRC01.
10. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence,

assessment of safety or infusion reactions, or a volunteer's ability to give informed consent

11. **Psychiatric condition that precludes compliance with the protocol.** Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
12. **Asthma**, other than mild, well-controlled asthma
13. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
14. **Malignancy** (Not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study)
15. **Seizure disorder:** History of seizure(s) within past three years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.
16. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema
17. History of **organ or tissue transplantation**
18. **Known hepatic or renal dysfunction**

5.3 Participant departure from infusion schedule or withdrawal

This section concerns an individual participant's departure from the infusion schedule. Pause rules for the trial as a whole are described in Section 10.3.

5.3.1 Delaying infusions for a participant

Under certain circumstances, a participant's scheduled infusion will be delayed. The factors to be considered in such a decision include but are not limited to the following:

- Prior to infusion, abnormal vital signs or clinical symptoms that may mask assessment of a study product reaction
- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delay or withdrawal from the infusion schedule. The investigator may consult with the HVTN 704/HPTN 085 PSRT.
- Pregnancy: for participants who become pregnant infusions will be stopped. If the participant is no longer pregnant (as demonstrated by a negative urine or serum pregnancy test) and wants to continue with infusions, the HVTN 704/HPTN 085 PSRT will be consulted to determine whether the participant may resume infusions or whether infusions should be permanently discontinued.

5.3.2 Participant departure from infusion schedule

Every effort should be made to follow the infusion schedule per the protocol. If a participant misses an infusion and the visit window period for the infusion has passed, then sites may consult the SSP.

5.3.3 Discontinuing infusions for a participant

Under certain circumstances, an individual participant's infusions will be permanently discontinued. Specific events that will result in stopping a participant's infusion schedule include:

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of infusions may be granted with the unanimous consent of the HVTN 704/HPTN 085 PSRT);
- Clinically significant condition (ie, a condition that affects the immune system or for which continued infusions and/or blood draws may pose additional risk), including but not limited to the following:
 - Any grade 4 local or systemic reactogenicity symptom or AE that is subsequently considered to be related to study product;
 - An SAE that is subsequently considered to be related to study product;
 - Any grade 3 clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to study product;
 - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product;
 - Clinically significant hypersensitivity reaction including but not limited to type 1 hypersensitivity reaction and/or serum sickness associated with study product. Consultation with the HVTN 704/HPTN 085 PSRT is required prior to subsequent infusion following any hypersensitivity reaction associated with study product; or
- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).

Infusions will be permanently discontinued for a participant diagnosed with HIV infection or with 2 reactive HIV tests, even if subsequent testing indicates that the participant is not HIV infected.

Participants for whom infusions are discontinued for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in Schedule 4 follow-up visits and protocol-specified procedures (see Appendix I and Appendix M), unless medically contraindicated.

5.3.4 Participant termination from the study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation

- Participant relocates and remote follow-up or transfer to another CRS is not possible
- CRS determines that the participant is lost to follow-up
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff)
- Any condition where termination from the study is required by applicable regulations.

6 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 1-1. See the IBs for further information about study products.

6.1 Study product regimen

The schedule of study product administrations is shown in Section 1 and additional information is given below.

Group 1

Treatment 1 (T1): VRC-HIVMAB060-00-AB 10 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 2

Treatment 2 (T2): VRC-HIVMAB060-00-AB 30 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 3

Control 3 (C3): Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) to be administered as a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

6.2 Study product formulation

VRC-HIVMAB060-00-AB [VRC01, Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB]

VRC01 will be provided as a sterile clear, colorless to yellow isotonic solution with no visible particles. Each vial contains 100 mg / mL of VRC-HIVMAB060-00-AB in formulation buffer. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and do NOT contain a preservative. The product should be stored frozen (-45°C to -10°C). The study products are described in further detail in the IB.

Prior to preparation, vials containing VRC01 must be removed from the freezer and thawed for a minimum of 1 hour at room temperature. Following this 1 hour thaw, the unopened vials of VRC01 may be stored for up to 24 hours at room temperature (not to exceed 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may NOT be thawed or stored in direct sunlight. Once thawed, product may NOT be refrozen.

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. These particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation has no effect on product quality. If the particles do not disappear at room temperature, the vials should be placed in the refrigerator, as particles may continue to dissipate at 2°C to 8°C (36°F to 46°F). Vials that continue to have visible particles after a maximum of 24 hours at controlled room temperature and/or after 4 weeks at 2°C to 8°C (36°F to 46°F) should not be used. Instead, those vials with particles still visible should be quarantined [at 2°C to 8°C (36°F to 46°F)] until they are returned to the CRPMC (or manufacturer upon request of the CRPMC) or destroyed if directed by the CRPMC.

Control for VRC01 [Sodium Chloride for Injection USP, 0.9%]

Sodium Chloride for Injection USP, 0.9% will be used as the Control for VRC01. It must be stored as directed by the manufacturer. For sites who do not have access to Sodium Chloride for Injection USP, 0.9%, the Sodium Chloride for Injection, 0.9% that they use must meet the following criteria: a sterile solution of Sodium Chloride in Water for Injection which contains no antimicrobial agents. It is nonpyrogenic and is intended for intravenous administration.

6.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription **MUST** contain the participant's weight based upon the participant's weight at the most recent visit where weight was measured (this includes screening) and randomization code (this may NOT be communicated verbally). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 38 General Chapter Physical Tests / <797> Pharmaceutical Compounding - Sterile, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

6.3.1 VRC-HIVMAB060-00-AB (10mg/kg IV) - (Group 1)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($10 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for up to 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 7 days if stored at 2°C to 8°C
- 30 hours if stored at room temperature (not to exceed 32°C)

Product may NOT be stored in direct sunlight.

(Note: Site pharmacists must follow their institutional policy if it is less than the information above).

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.2 VRC-HIVMAB060-00-AB (30mg/kg IV) - (Group 2)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($30 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will then add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 7 days if stored at 2°C to 8°C
- 30 hours if stored at room temperature (not to exceed 32°C)

Product may NOT be stored in direct sunlight.

(Note: Site pharmacists must follow their institutional policy if it is less than the information above).

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.3 Control for VRC01 (Group 3)

To prepare an IV infusion, the pharmacist, using aseptic technique, will add 50 mL of Sodium Chloride for Injection USP, 0.9% to a 100 mL bag of Sodium Chloride for Injection USP, 0.9%. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 7 days if stored at 2°C to 8°C
- 30 hours if stored at room temperature (not to exceed 32°C)

Product may NOT be stored in direct sunlight.

(Note: Site pharmacists must follow their institutional policy if it is less than the information above).

6.4 Administration

VRC01 or Control (Intravenously)

Prior to infusion, if the VRC01 or Control IV bag has been stored at 2°C to 8°C, the bag should be equilibrated to room temperature (maximum of 32°C) for 30 minutes and may be additionally held for up to 24 hours prior to and during product administration. (NOTE: This 24 hour period may NOT exceed the DO NOT INFUSE after date and time on the IV bag label.)

The IV bag prepared by the pharmacy will include the participant’s weight that was used for preparation of the IV bag (VRC01 or Control). The clinician responsible for administration will check the bag label and confirm that the participant identifier is correct and that the weight is the correct weight for preparation for that visit (refer to Section 6.3 for more information).

The investigational study product solution will typically be administered IV over about 30 to 60 minutes using a volumetric pump of 150 mL. The total time needed to administer the dose may be longer based on factors such as participant tolerance.

6.5 Acquisition of study products

VRC-HIVMAB060-00-AB is provided by the VRC/DAIDS/NIAID.

Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) will not be provided through the protocol and must be obtained by the site.

Once a CRS is protocol registered, the pharmacist can obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) by following the ordering procedures given in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

6.6 Pharmacy records

The CRS pharmacist is required to maintain complete records of all study products. The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

6.7 Final disposition of study products

All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the CRPMC. The procedures and relevant form are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

7 Clinical procedures

The schedules of clinical procedures are shown in Appendix J through Appendix M.

7.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The informed consent form documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in this study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the participant and the review should be documented. At each study visit, CRS staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information is learned that might affect the participants' decisions to stay in the trial, this information will be shared with trial participants. If necessary, participants will be asked to sign revised informed consent forms.

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to their Institutional Review Board/Ethics Committee (IRB/EC) and any applicable Regulatory Entity (RE) for human subjects protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is “Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs [informed consent forms] prior to implementation at a site.” CRSs are responsible for knowing the requirements of their applicable REs.

7.1.1 Screening consent form

Without a general screening consent, screening for a specific study cannot take place until the site receives protocol registration from the DAIDS RSC Protocol Registration Office.

Some CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV prevention trial. In this way, CRS staff can continually screen potential participants and, when needed, proceed quickly to obtain protocol-specific enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time period specified in the eligibility criteria.

7.1.2 Protocol-specific consent forms

The protocol-specific consent forms describe the study products to be used and all aspects of protocol participation, including screening and enrollment procedures. A sample protocol-specific consent form for the main study is located in Appendix A. A separate sample consent form for other uses of specimens is located in Appendix C.

Each CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in Appendix A and Appendix C. The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC, and any applicable RE
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their site-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the level of understandability.

The sample informed consent form includes instructions throughout the document for developing specific content.

Sites should follow the instructions in the Protocol-specific Official Memo distributed along with this protocol regarding when they may begin using their site-specific protocol consent forms.

Regarding protocol registration, sites should follow procedures outlined in the current version of the DAIDS Protocol Registration Manual.

7.1.3 Assessment of Understanding

Study staff are responsible for ensuring that participants fully understand the study before enrolling them. This process involves reviewing the informed consent form with the participant, allowing time for the participant to reflect on the procedures and issues presented, and answering all questions completely.

An Assessment of Understanding is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary. Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

IRB/EC and any applicable RE may require that a participant has signed either a screening or protocol-specific consent document prior to administering the Assessment of Understanding. The consent process (including the use of the Assessment of Understanding) should be explained thoroughly to the IRB/EC and any applicable RE, whose recommendations should be followed.

7.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before infusion on Day 0. All inclusion and exclusion criteria must be assessed within 56 days before enrollment, with the exception of HIV testing, which must be performed within 30 days before enrollment (see Section 5.1), unless otherwise specified in the eligibility criteria (or below in this section).

After the appropriate informed consent has been obtained and before enrollment, the following procedures are performed:

- Medical history, documented in the case history record;
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots (record the complete generic name for all medications);
- Laboratory tests as defined in the inclusion and exclusion criteria, including:
 - Screening HIV testing at local lab (see SSP)
 - CBC with differential
 - ALT
 - Creatinine
 - Urine dipstick
 - Urine or serum pregnancy test (volunteers capable of becoming pregnant); Persons who are not capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Assessment of participant risk for HIV infection
- Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>);
- Counseling on HIV testing and risk reduction, performed in compliance with US CDC current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 7.5; and
- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in the study inclusion criteria and in Appendix B. Discussion of pregnancy prevention includes advising a participant who is capable of becoming pregnant but who reports no current sexual activity that could lead to pregnancy to have a plan to begin adequate birth control. This plan would be put to use if, during

the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

7.2.1 Use of screening results from another HVTN or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this study, and the tests were conducted within the time periods specified in the eligibility criteria (see Section 5).

7.3 Enrollment and infusion visits

Enrollment is simultaneous with first infusion. The time interval between randomization and enrollment should not exceed 4 working days. The CRS requests the randomization assignment from the Web-based randomization system. Circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all infusion visits, the following procedures are performed before infusion:

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Assessment of baseline reactogenicity parameters;
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- Assessment of concomitant medications (as described in Section 7.2);
- ALT;
- Creatinine;
- CBC with differential;
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Blood collection for HIV testing and sample storage.

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (see Sections 6.3 and 6.4).

Administration of an infusion and infusion-related procedures must be accomplished within 1 calendar day.

Immediately following the first infusion, the participant remains in the clinic for observation and initial reactogenicity assessment. See the SSP for details regarding infusion visit protocols and subsequent infusion observation and reactogenicity assessment procedures that CRSs must follow. Before leaving the clinic, the participant is given the postinfusion symptom log and is instructed on how to complete it. The site will make arrangements to obtain a report of reactogenicity events from the participant after the 3-day reactogenicity period (as described in Section 7.10 and in the SSP).

The following procedures will be performed at all infusion visits. These procedures may be performed prior to, during, or following infusion:

- Administration of the participant questionnaire which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling);
- Risk reduction counseling (as described in Section 7.5);
- For participants capable of becoming pregnant, pregnancy prevention assessment (as described in Section 7.2 and 7.6);
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.
- Additional procedures will be performed at scheduled visits as specified in Appendix I:
 - Syphilis serology testing,
 - Gonorrhea (GC)/chlamydia (CT) testing by urine, and rectal and oropharyngeal swabs, and
 - Urine dipstick (see Section 7.9).

7.4 Post-infusion visits for HIV-uninfected study participants

The following procedures are performed at all post-infusion follow-up visits for HIV-uninfected study participants:

- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Blood collection for HIV testing and sample storage; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled follow-up visits as specified in Appendix F and Appendix J:

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Administration of participant questionnaire, which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling)
- Risk reduction counseling (as described in Section 7.5);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- For participants who are capable of becoming pregnant, pregnancy prevention assessment (as described in Section 7.2 and 7.8);
- Assessment of new or unresolved AEs/intercurrent illnesses;
- Urine dipstick (see Section 7.9); and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.5 HIV counseling and testing

HIV counseling will be performed in compliance with the CDC's guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the protocol-specific HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection. In addition, study participants will be provided with HIV prevention supplies and referral to providers of PrEP per local and regional guidelines. Study investigators will ensure that participants have access to standards of care for HIV prevention in their local settings. As new data emerge and standards of care for HIV prevention evolve, both the content of risk reduction counseling and referrals for biomedical interventions will be updated to conform to current best practices for the populations enrolled in this trial. For additional details regarding PrEP provision and referrals, see the HVTN 704/HPTN 085 website.

7.5.1 Study product–related seroreactivity

Human sera containing purified VRC01 at concentrations up to 1600 mcg/mL have been tested using a variety of commercially available HIV test kits without any indication of reactivity. For this reason, we do not anticipate that receipt of VRC01 will cause a reactive result on currently available HIV test kits, but this remains a theoretical possibility.

Because this possibility cannot be categorically eliminated, study staff will advise study participants to confine their HIV testing while in the study to that provided through the CRS. Staff will also inform study participants of the likelihood of routine HIV testing being offered or performed outside the study CRS at emergency rooms, clinics, and medical offices and will inform participants of their right to opt out of HIV testing outside the study site. CRS staff should inform study participants if local and/or state/regional policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline HIV testing preemptively. CRS staff should also inform participants if positive HIV test results must be reported to local public health authorities. CRS staff should also inform participants of the need to maintain study blinding by getting HIV testing only at the study CRS. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV mAb clinical trial and should only be tested for HIV at the study CRS.

Study staff should also stress that the study product is completely cleared from the body within a few months, so even the theoretical risk of VRC01 causing a misleading HIV test result will disappear before their final scheduled clinic visit.

7.6 Follow-up visits for HIV-infected participants

The following procedures are performed at scheduled follow-up visits as specified in Appendix G, Appendix H, Appendix K, and Appendix L:

- Counseling on HIV testing and diagnosis;
- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- ART assessment;
- Assessment of concomitant medications (as described in Section 7.2);
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV transmission risk reduction counseling;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, viral load testing, VRC01 Ab levels, functional assays, viral isolation/sequencing, and sample storage (see Appendix G, Appendix H, and Section 8.5);
- Blood collection for CD4+ T cell counts;
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and

- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.7 Follow-up visits for participants who discontinue infusions for reasons other than HIV infection

Participants for whom infusions are discontinued for reasons other than HIV infection should be encouraged to continue in the study. For such participants, the following procedures are performed at approximately quarterly scheduled follow-up visits as specified in Appendix I and Appendix M:

- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- Risk reduction counseling (as described in Section 7.5);
- Assessment of concomitant medications (as described in Section 7.2);
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, CBC/differential, ALT, creatinine, VRC01 Ab levels, functional assays, and sample storage (see Appendix I and Appendix M);
- Urine dipstick (see Section 7.9);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.8 Contraception status

Contraception status is assessed and documented at screening and infusion visits for a participant who is capable of becoming pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive

methods. These participants should be reminded regularly of the importance of using contraception and should be referred to specific counseling, information, and advice as needed. (See Appendix B for further detail.) This reminder should be documented in the participant's study record.

Infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation—must be documented in the participant's study record.

7.9 Urine testing

Urine dipstick testing may be performed in the clinic or the lab. The following analytes should be analyzed and recorded: specific gravity, protein, blood/hemoglobin, pH, urobilinogen, bilirubin, ketone, leucocyte esterase, nitrite, and glucose. The examination is performed on urine obtained by clean catch. Urine microscopy is required when the protein result is 1+, 2+, 3+, or 4+ (or semi-quantitative 30, 100, 300, or 2000 g/L) and/or the blood/hemoglobin result is trace, 1+, 2+, 3+, or 4+, but not required (unless otherwise clinically indicated) if the dipstick result is abnormal due to non-urinary bleeding.

If the dipstick is transiently abnormal due to non-urinary bleeding (eg, uterine or vaginal bleeding or spotting) or infection, document this issue in the participant's source documentation. For infection, provide appropriate treatment and/or referral. If the dipstick was performed for screening then repeat the dipstick following resolution and, if within the eligibility limits specified in the protocol, the participant may be enrolled. See SSP for further detail.

A follow-up urine test should be deferred if a participant is experiencing non-urinary bleeding (eg, menstruation), but should be performed as soon as possible. If a follow-up dipstick is abnormal due to non-urinary bleeding (eg, a participant's menstrual period), document in the comment section of the CRF and repeat the dipstick once the participant is no longer experiencing non-urinary bleeding. In this case, a urine microscopy is not required (see SSP for further detail).

7.10 Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after infusions per the SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, except as noted in Section 10.2.2.

The reactogenicity assessment period is 3 full days following each infusion. Participants are instructed to record symptoms using a postinfusion symptom log. The site staff and the participant will be in contact after the 3-day reactogenicity period, or sooner if indicated, to review reactogenicity data. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. Participants are instructed to contact the clinic for events that arise during the period between infusion and the next scheduled visit. In general, a participant who self-reports any postinfusion reaction

greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity events are reported using CRFs that correspond to the time of assessment per the SSP. Reactogenicity assessments include assessments of specific systemic and local signs and symptoms and infusion site reactions. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of infusion and 3 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse event log form.

7.10.1 Assessment of systemic and local signs and symptoms

Systemic signs and symptoms include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, and vomiting. Local symptoms include pain and/or tenderness proximal to the infusion site. The maximum severity reached for each symptom during the assessment period per the SSP is reported.

7.10.2 Assessment of infusion site

Infusion site reactions may include redness/erythema and induration/swelling. The maximum horizontal and maximum vertical measurements for infusion site redness/erythema and induration/swelling are recorded.

All infusion site reactions are monitored until resolution. Areas greater than 25 cm² are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

7.11 Visit windows and missed visits

Visit windows are defined in the SSP. For a visit not performed within the window period, a Missed Visit form is completed.

If a participant misses a scheduled visit, CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. See the HVTN 704/HPTN 085 SSP for more details. If a participant missed an infusion visit or if infusions must be permanently discontinued, see Section 5.3.2 and Section 5.3.3 for resolution.

7.12 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, ALT, and Creatinine), pregnancy testing, social impact assessment, and HIV test.

7.13 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given during the pregnancy, but remaining visits and study

procedures should be completed unless medically contraindicated. For participants who are no longer pregnant, see Section 5.3.1. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome.

8 HIV infection assessment and clinical response

8.1 HIV symptom assessment

At all scheduled visits and at unscheduled visits due to illness or suspected exposure, if necessary, information will be collected about any signs or symptoms suggestive of acute HIV infection. Participants will be counseled about signs and symptoms of acute HIV infection and at visits following recent high-risk exposure, participants will be queried about any signs/symptoms suggestive of acute HIV infection. Presence of signs/symptoms suggestive of acute HIV infection, an intercurrent illness consistent with acute retroviral syndrome, or history of high-risk exposure would prompt a diagnostic work-up per the protocol-specific algorithm for recent exposure to determine HIV infection.

8.2 HIV screening test (prior to randomization)

Prior to randomization, participants will be screened for HIV-1/2 infection by FDA-approved blood tests (non-US sites may use locally available assays that have been approved by HVTN and HPTN Laboratory Operations [see SSP]). Volunteers identified as being HIV infected during screening will be referred for medical treatment and management of the HIV infection. These individuals may also be referred to appropriate ongoing clinical trials or observational studies. For volunteers who have one or more reactive/positive HIV tests, but whose HIV status is inconclusive, any further testing will be performed locally.

8.3 HIV testing postinfusion

Following enrollment, HIV testing will take place at scheduled clinic visits (Appendix F).

HIV testing will be performed using the protocol-specific HIV testing algorithms (see SSP). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV 1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV 1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit (ie, visit #.X specified in Appendix G and Appendix H). Samples to be stored for future studies will also be collected at this time (see Appendix G).

A 'case' will be defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s) (Section 8.4).

The HVTN Laboratory Program is responsible for all in-study diagnostic testing.

8.4 Endpoint adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess. Therefore, this study will have an endpoint adjudication process to review all serological and virological test results in a blinded manner for each participant who tests positive per the HVTN 704/HPTN 085 HIV diagnostic testing algorithms. Adjudicators will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (ie, HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the VRC and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

8.5 HIV infection during the study

It is critical to the success of the study that HIV-infected participants be properly identified and all data postdiagnosis be carefully recorded. Information obtained from these cases of HIV-1 infection will form the basis of the primary endpoint assessment.

Participants who develop HIV infection following the initial infusion of study product may remain in the study for follow-up but will receive no further infusions. This includes participants for whom infusions were discontinued for reasons other than HIV infection but for whom HIV-1 infection has subsequently been confirmed. All participants who become HIV-1-infected following enrollment through their final study visit will be monitored as indicated in Appendix G and Appendix K.

If a participant is confirmed to have become HIV infected after enrollment, plasma HIV-1 RNA will be measured on archived samples prior to the first positive screening test. HIV-1 RNA testing will also be performed at 2-week intervals up to 8 weeks postdiagnosis, then at 12 and 24 weeks postdiagnosis. In addition to plasma HIV-1 RNA testing, participants will also have specimens drawn for measurements of VRC01 Ab serum levels, neutralization and other antibody functions, viral isolation and sequencing; physical exams, recording of AEs, counseling to reduce HIV transmission risk, and social impact assessments will also be performed at most of these visits.

Longer-term follow-up for these participants may be accomplished through enrollment in another protocol. Archived samples from earlier visits may also be tested to determine the earliest date of HIV infection.

If enrollment visit HIV testing indicates that a participant was HIV infected at enrollment (ie, prior to the first infusion of study product) or a participant is diagnosed with HIV-2 infection following enrollment, then the procedures indicated in the preceding paragraph do not apply. Such participants should be followed as indicated in Appendix H and Appendix L. This also applies to participants for whom infusions are discontinued for reasons other than HIV infection and who subsequently are diagnosed with HIV-2 infection.

8.6 Medical care for participants who become HIV infected

It is anticipated that some study participants, whether they are randomized to receive VRC01 or control, will become HIV infected during the course of the trial. It is critical that these HIV-infected participants receive appropriate medical care.

The investigators associated with this trial will refer participants who develop HIV infection while participating in this trial to medical professionals for care.

9 Laboratory

9.1 CRS laboratory procedures

The SSP provides further guidelines for operational issues concerning the clinical and processing laboratories. The manual includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix F through Appendix I. For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, laboratory special instructions will be posted on the protocol-specific section of the HVTN website.

9.2 Total blood volume

Required blood volumes per visit are shown in Appendix F through Appendix H. Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

9.3 Assay timepoints

Endpoint assays are performed on participants at the timepoints shown in Appendix F through Appendix I may be performed at baseline. Assays for humoral and cellular responses may be performed on participants or a subset of participants at other timepoints; the schedules are shown in Appendix F through Appendix I.

9.4 VRC01 mAb levels

VRC01 levels will be measured in serum. An ELISA will be used to determine the concentration of the VRC01 antibody in the serum. The ELISA employs the VRC01 Fab-specific 5C9 mAb, which is an anti-idiotypic antibody cloned from a single B cell that was sorted by flow cytometry using a VRC01 scFv probe. The 4-parameter logistic curve regression of a standard curve of VRC01 covering the range from 0.031 to 1.0 mcg/mL is utilized in this assay to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay. This assay has been qualified but not formally validated. The functional sensitivity for the generation of the ELISA assay format, which is currently used at NVITAL, is 2 mcg/mL and as the technology for this assay continues to develop, an updated assay may be utilized.

9.5 Endpoint assays: humoral

9.5.1 Anti-VRC01 antibody assay

Assessment for development of anti-VRC01 antibodies in participants will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. The assay uses biotin-labeled VRC01 immobilized on a streptavidin-coated MSD plate as the capture molecule, and the SULFO-TAG labeled VRC01 as the reporter molecule. This assay is independent of the anti-VRC01 antibody isotype, and permits the detection of both high and low affinity antibodies.

9.5.2 Neutralizing antibody assay

Depending upon the VRC01 concentrations measured in collected specimens, their capacity to neutralize HIV in blood and mucosal secretions may be evaluated by an in vitro cell-based virus neutralization assay [130-132] using pseudotyped viruses. All specimens testing positive for anti-VRC01 antibodies will be tested for HIV-1 neutralizing activity.

One or more viruses that are among the most sensitive to VRC01 (eg, MN.3 and MW965.26) will be assayed. The IC_{50} of VRC01 against both of these viruses is 0.01 – 0.03 mcg/ml and the TZM-bl assay is validated for this level of sensitivity.

9.6 ARV detection

A direct, biomedical measure will be used to assess ARV use in this study. This approach will be used, since self-report of ARV use for PrEP or PEP and other purposes has been shown to be unreliable in a variety of settings [118,119,133]. For this study, ARV testing will be performed using a low cost, high-throughput, qualitative multi-drug assay developed at the HPTN Laboratory Center. This approach will allow detection of drugs that are FDA-approved for PrEP (FTC/TDF) as well as numerous other ARVs that may be used off-study/off-label for a variety of reasons (eg, PrEP, PEP, recreational use, hepatitis treatment). Testing will be performed retrospectively on batched samples. Individual test results will not be returned to study sites or study participants.

The methods that will be used for ARV testing are summarized here. Stored serum or plasma samples collected in the study will be tested for the presence of approximately 20 ARVs using an assay based on high resolution mass spectrometry (HRMS) analysis. The following ARVs were included in the assay when this document was prepared: 9 protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir), 6 NRTIs (abacavir, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine), 3 NNRTIs (efavirenz, nevirapine, rilpivavirine), an integrase inhibitor (raltegravir), and an entry inhibitor (maraviroc). Each drug is identified and reported separately. The current limit of identification for each of the ARVs listed above is 10 ng/mL. The specific methods used for ARV detection may be modified (eg, to improve throughput) before samples from this study are tested.

9.7 Host (human) genotyping

Various markers, such as genes associated with host immune functions or HIV disease progression may also be assessed.

9.8 Lab assay algorithm

The HVTN Lab Assay Algorithm lists assays that characterize various types of immunologic activity as well as host genetics that may be conducted to characterize the drug activity in this study. Various types of assays may be employed to assess maintenance of functional drug activity at multiple timepoints selected based on drug level outcomes. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

9.9 Possible additional studies

Samples may be used for other testing and research related to furthering the understanding of HIV immunology, monoclonal antibodies, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

9.10 Other use of stored specimens

The Networks store specimens from all study participants indefinitely, unless a participant requests that specimens be destroyed or if required by IRB/EC or RE.

Other use of specimens is defined as studies not described in the protocol.

This research may relate to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases. This could include limited genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other testing on specimens will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs if required.

The protocol sample informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study site investigator or designee must notify HVTN Regulatory Affairs in writing. In either case, HVTN Regulatory Affairs directs the HVTN Lab Program not to use samples from these participants for such other uses.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on other use of specimens.

9.11 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

10 Safety monitoring and safety review

10.1 Safety monitoring and oversight

10.1.1 HVTN 704/HPTN 085 PSRT

The HVTN 704/HPTN 085 PSRT is composed of the following members:

- DAIDS medical officer representatives,
- Protocol chairs and cochairs,
- Protocol Team leader,
- Core medical monitor,
- Clinical safety specialist (CSS), and
- Regional medical liaison (RML).

A medical officer from an organization(s) designated by the study sponsor will also participate in the PSRT.

The clinician members of HVTN 704/HPTN 085 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinators, project managers, study product developer representatives, clinical research manager, clinical trial manager, and others may also be included in HVTN 704/HPTN 085 PSRT meetings.

10.1.2 NIAID DSMB

The NIAID DSMB assesses the effects of the study product during the trial, provides other monitoring as described in Section 4.9.1.1, and may give advice to the HVTN 704/HPTN 085 Oversight Committee.

10.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 704/HPTN 085 PSRT and NIAID DSMB.

The roles and responsibilities of the HVTN CSS or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 704/HPTN 085 PSRT AE review criteria (see Section 10.3);
- Notifying CRSs and other groups when safety pauses are instituted and lifted (see Section 10.3);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 704/HPTN 085 PSRT.

10.2 Safety reporting

10.2.1 Submission of safety forms to SDMC

Sites must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, concomitant medications) before the end of the next business day after receiving the information. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information.

10.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation subject administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). The AE reporting period for this study comprises the entire study period for each individual participant (from study enrollment until study completion or discontinuation of the study). All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014], available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>, except that the AEs below will be reported according to the SSP:

- Weight loss
- Infusion Site Erythema or Redness and Infusion Site Induration or Swelling
- Insomnia

As detailed in the SSP, two additional parameters, cytokine release syndrome and serum sickness, have been added to the DAIDS AE Grading Table for HVTN 704/HPTN 085.

AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (Section 10.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 10.2.4).

Sites are expected to notify the CSS or RML of any serious safety concern requiring their attention (see Table 10-1). Telephone numbers and email addresses are found on the HVTN704/HPTN 085 protocol-specific website. Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, the CSS or RML will reply during working hours (ie, US Pacific Time or South African Standard Time) to confirm that the email has been received and reviewed. If email service is not available, the CRS should notify the CSS or RML of the event by telephone, then submit CRFs.

In addition, site investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

10.2.3 Expedited reporting of adverse events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE Manual), which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AE reports by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about expedited AE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

Under ICH E2A (*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*), an SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe),
- requires patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is a medically important event or reaction.

Medical and scientific judgment should be exercised when deciding if other situations are serious. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions not resulting in hospitalization, or development of drug dependency or drug abuse.

The expedited reporting period for this study comprises the entire study period for each individual participant (from study enrolment until study completion or discontinuation from the study).

The study products for which expedited reporting are required are:

- VRC01, and
- Control.

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

If the PSRT believes unblinding of the site PI to treatment assignment will assist with the clinical management of the SAE, the PSRT may consult the independent NIAID DSMB for a recommendation. In the event the PSRT and/or the NIAID DSMB determines that unblinding is indicated, the unblinded statistician, DSMB Chair, or designee will inform the site physician of the participant's treatment assignment in such a manner as to maintain the study blind of the PSRT and study team. For additional impact and management of SAEs on the study, refer to Section 10.3.

10.2.4 Expedited reporting of AEs to pertinent national regulatory authorities

The study sponsor or designee(s) prepares and files expedited reports to appropriate regulatory authorities within the timelines required by pertinent national regulatory authorities.

Site IoRs/designees will submit AE information and any other relevant safety information to their ECs/IRBs in accordance with EC/IRB requirements.

10.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and infusion with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 704/HPTN 085 PSRT AE review are summarized in Table 10-1. Infusions may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the

HVTN 704/HPTN 085 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of infusions are listed in Section 5.3.

Table 10-1 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	CRS action ^a	HVTN Core ^b action
SAE, related	Grade 4 or 5	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 704/HPTN 085 PSRT notification
SAE, related	Grade 3	E-mail and submit forms immediately	Prompt HVTN 704/HPTN 085 PSRT AE review to consider pause
AE ^c , related	Grade 4 or 3	Email and submit forms immediately	Prompt HVTN 704/HPTN 085 PSRT AE review to consider pause

^a Phone numbers and email addresses are found on the Protocol home page on the HVTN Members' site (<https://members.hvtn.org/protocols/hvtn704/HPTN085>).

^b HVTN CSS or HVTN Core designee

^c Does not include subjective reactogenicity symptoms (injection site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea).

For all safety pauses, HVTN Core notifies the HVTN 704/HPTN 085 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN and HPTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the NIAID DSMB.

Once a trial is paused, the HVTN 704/HPTN 085 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of infusions is appropriate, consulting the NIAID DSMB if necessary. HVTN Core notifies the participating HVTN and HPTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study infusions. Based on the HVTN 704/HPTN 085 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 704/HPTN 085 PSRT notification or prompt HVTN 704/HPTN 085 PSRT AE review is triggered, HVTN Core notifies the HVTN 704/HPTN 085 PSRT as soon as possible during working hours (US Pacific Time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 704/HPTN 085 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and an applicable RE protocol-related safety information (such as IND safety reports, notification of study product holds due to the pause rules, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 704/HPTN 085 PSRT (see Section 10.4.2).

10.4 Review of cumulative safety data

Routine safety review occurs at the start of enrollment and then throughout the study.

Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and include queries to the CRSs. Events are tracked by internal reports until resolution.

10.4.1 Daily review

Blinded daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 704/HPTN 085 PSRT AE review criteria.

10.4.2 Twice monthly review

During the infusion phase of the trial, the HVTN 704/HPTN 085 PSRT reviews clinical safety reports twice each month and conducts calls to review the data as appropriate. After the infusions and the final postinfusion safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 704/HPTN 085 PSRT. The HVTN CSS or HVTN Core designee reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

10.4.3 DSMB review of cumulative safety data

The DSMB will periodically review accumulating safety data by masked treatment group. Prior to each such review, the SDMC will provide the DSMB with data as described in Section 4.9.1. Reports will be cumulative, generated from an up-to-date data file. Reports will show the data coded by treatment group; however, upon request of the DSMB, the SDMC will provide the Board with the actual treatment group.

10.5 Study termination

This study may be terminated early by NIAID upon recommendation by the DSMB, a pertinent national regulatory authority, Office for Human Research Protections (OHRP), or study product developer. In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

10.6 Social impact reporting

It is possible that participants' involvement in the study could result in social impacts. For example, a participant's involvement in the study could become known to others, and a social harm may result (ie, because participants could be perceived as being HIV infected or at "high risk" for HIV infection). Participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Alternatively, a social benefit may result (eg, a participant could feel good helping others).

Social harms are negative social impact events and social benefits are positive social impact events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. Social impacts will be collected and reported on CRFs during scheduled visits (see Appendix J through Appendix M). A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. While maintaining participant confidentiality, study sites may engage their Community Advisory Board (CAB) in exploring the social context surrounding instances of social harms to minimize the potential occurrence of such an impact.

11 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with Good Clinical Practice (GCP) (ICH6), the HVTN and HPTN network-specific *Manuals of Operations*, and DAIDS Clinical Research Policies and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Ancillary studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the SSP.

11.1 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site should contact the participant first, and then notify the IRB/EC and any applicable RE of the matter as soon as possible.

12 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of clinical trials. The HVTN and HPTN (hereafter, referred to as the “Networks”) have addressed ethical concerns in the following ways:

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for preventing HIV infection, using methods that are scientifically rigorous and valid, and in accordance with GCP guidelines.
- Network scientists and operational staff incorporate the philosophies underlying major codes [134-136], declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV prevention clinical trials.
- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. CABs are required by DAIDS and supported at all Network research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines [137].
- Network clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
- The Networks require that all international Network sites lacking national plans for providing ART develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants will be referred to programs for ART provision when the appropriate criteria for starting ART are met. If a program is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.
- The Networks agree that appropriate referrals for access to PrEP and PEP should be provided according to national and/or local guidelines.
- The Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.
- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.
- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.

- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.
- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.
- The Networks recognize the importance of institutional review and values the role of in country IRBs, ECs, and any applicable REs as custodians responsible for ensuring the ethical conduct of research in each setting.

13 IRB/EC/RE review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs to ensure that certain requirements are satisfied on initial and continuing review of research (Title 45, Code of Federal Regulations (CFR), Part 46.111(a) 1-7; 21 CFR 56.111(a) 1-7). The following section highlights how this protocol addresses each of these research requirements. Each Network Investigator welcomes IRB/EC and any applicable RE questions or concerns regarding these research requirements.

This trial is being conducted in North and South America with funding from the US NIH. Due to this, the trial is subject to both US and local regulations and guidelines on the protection of human research subjects and ethical research conduct. Where there is a conflict in regulations or guidelines, the regulation or guideline providing the maximum protection of human research subjects will be followed.

In compliance with international and local (as appropriate) GCP, each research location has a locally based Principal Investigator (PI) who is qualified to conduct (and supervise the conduct of) the research; and the research addresses an important local health need for an HIV prevention method. In addition, the investigators take responsibility for the conduct of the study and the control of the study products, including obtaining all appropriate regulatory and ethical reviews of the research. Each participating site has a standard operating procedure for ensuring that participants have the necessary information to make a decision whether or not to consent to the research.

The sections below address each of the review concerns by IRBs/ECs and any applicable REs regarding how the research will be conducted.

13.1 Minimized risks to participants

45 CFR 46.111 (a) 1 and 21 CFR 56.111 (a) 1: Risks to subjects are minimized.

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants following study product administration and collecting information regarding side effects for several days following study product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product infusions, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use (for participants capable of becoming pregnant); and (f) providing safety monitoring.

13.2 Reasonable risk/benefit balance

45 CFR 46.111(a) 2 and 21 CFR 56.111(a) 2: Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a healthy participant are not as apparent as they would be in treatment protocols, where a study participant may be ill and may have exhausted all conventional treatment options. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

13.3 Equitable subject selection

45 CFR 46.111 (a) 3 and 21 CFR 56.111 (a) 3: Subject selection is equitable

This protocol has specific inclusion and exclusion criteria for investigators to follow in admitting participants into the protocol. Participants are selected because of these criteria and not because of positions of vulnerability or privilege. Investigators are required to maintain screening and enrollment logs to document volunteers who screened into and out of the protocol and for what reasons.

13.4 Appropriate informed consent

45 CFR 46.111 (a) 4 & 5 and 21 CFR 56.111 (a) 4 & 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section 7.1). Each site is provided training in informed consent by the Networks as part of its entering the respective Network. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

13.5 Adequate safety monitoring

45 CFR 46.111 (a) 6 and 21 CFR 56.111 (a) 6: There is adequate provision for monitoring the data collected to ensure the safety of subjects.

This protocol has extensive safety monitoring in place (Section 10). Safety is monitored daily by the HVTN CSS or HVTN Core designee and routinely by the HVTN 704/HPTN 085 PSRT. In addition, a DSMB periodically reviews study data.

13.6 Protect privacy/confidentiality

45 CFR 46.111 (a) 7 and 21 CFR 56.111 (a) 7: There are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term "privacy" concerns research participants or potential research participants as individuals whereas the term "confidentiality" is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see Appendix A). The privacy of participants is protected by assigning unique identifiers in place of the participant's name on study data and specimens. In the United States, research participants in Network protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data/Specimens with the Networks and each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

14 Version history

The Protocol Team may modify the original version of the protocol. Modifications are made to Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 704/HPTN 085 are described below.

Protocol history and modifications

Date: March 9, 2016

Protocol version: 1.0

Protocol modification: Original protocol

15 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at <http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf>.
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/>
- Division of AIDS Protocol Registration Manual. Available at <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/prmanual.pdf>
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.0 [November 2014]. Available at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <http://rsc.tech-res.com/safetyandpharmacovigilance/manualforexpeditedreporting.aspx>
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 704/HPTN 085 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 704/HPTN 085 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN Laboratory Manual of Operations. Accessible through the HVTN website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/publications/dgr/Pages/index.aspx>.
- HVTN Lab assay algorithm
- HVTN algorithm for diagnosis of HIV infections. Part of the HVTN Site Lab Reference Manual (see above).

- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>
- HVTN 704/HPTN 085 Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.
- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>.
- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at <https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx>
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

See Section 17 for literature cited in the background and statistics sections of this protocol.

16 Acronyms and abbreviations

Ab	antibody
Ad	adenovirus
ACASI	audio computer assisted self-interview
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADCVI	antibody-dependent cellular viral inhibition
AIA	anti-idiotypic antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
BLI	BioLayer Interferometry
BMI	body mass index
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHO	Chinese hamster ovary
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence intervals
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CRS*	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	(NIAID) Data and Safety Monitoring Board
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EC ₅₀	effective concentration (50%)
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration

FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
GC	gonorrhea
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPTN	HIV Prevention Trials Network
HRMS	high resolution mass spectrometry
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
IC ₅₀	inhibitory concentration (50%)
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IPEC	Instituto de Pesquisa Clinica Evandro Chagas
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LANL	Los Alamos National Laboratory
LC	Laboratory Center
LOC	Leadership and Operations Center
mAb	monoclonal antibody
MITT	modified intent-to-treat
MOP	Manual of Operations
MPER	membrane proximal external region
MSM	men who have sex with men
MTF	male-to-female
nAb	neutralizing antibody
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NICD	National Institute for Communicable Diseases (Johannesburg, South Africa)
NIH	US National Institutes of Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NVITAL	NIAID Vaccine Immune T-Cell Antibody Laboratory
OBA	NIH Office of Biotechnology Activities

OC	Oversight Committee
OHRP	US Office for Human Research Protections
PAB	DAIDS Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	prevention efficacy
PEP	postexposure prophylaxis
PI	Principal Investigator
PK	pharmacokinetic
PMTCT	prevention of mother-to-child (HIV) transmission
PNG	potential N-linked glycosylation
PrEP	pre-exposure prophylaxis
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PYR	person year
RAB	DAIDS Regulatory Affairs Branch
RAC	NIH Recombinant DNA Advisory Committee
RE	regulatory entity
RPR	rapid plasma reagin
RSC	(DAIDS) Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SIV	simian immunodeficiency virus
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study specific procedures
STI	sexually transmitted infection
TasP	treatment as prevention
TCID ₅₀	tissue culture infectious dose (50%)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TG	transgender
tMLE	targeted maximum likelihood estimation
TPP	target product profile
TTNI	time to target number of infections
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VRC	Vaccine Research Center (NIAID)

VRP Vaccine Research Program
WHO World Health Organization

* CRSs were formerly referred to as HIV Vaccine Trial Units (HVTUs). Conversion to use of the term CRS is in process, and some HVTN documents may still refer to HVTUs.

17 Literature cited

1. UNAIDS. Report on the Global AIDS Epidemic, 2012 country progress reports. <http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/>. 2013. Last accessed: 2-20-2013
2. UNAIDS. Global Report: Report on the global AIDS epidemic 2013. **2013**;UNAIDS / JC2502/1/E.
3. WHO in partnership with UNICEF and UNAIDS. Global Report on HIV Treatment 2013: Results, Impact and Opportunities. **2014**.
4. UNAIDS. Local Epidemics Issues Brief. **2014**.
5. HIV/AIDS Fact Sheet. **11-2015**. <http://www.who.int/mediacentre/factsheets/fs360/en/>, accessed February 8, 2016.
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de BG, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **2011**;365:493-505.
7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* **2010**;363:2587-99.
8. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: Limitations to Treatment Safety and Efficacy: Adverse Effects of Antiretroviral Agents. <http://aidsinfo.nih.gov/guidelines>. 5-1-2014. Last accessed: 2-17-2015
9. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* **2012**;26:F13-F19.
10. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clin Infect Dis* **1992**;14:580-6.
11. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2006**;55:1-23.
12. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. *Curr Opin HIV AIDS* **2015**;10:129-34.

13. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* **1998**;102:531-7.
14. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, Connor EM, Losonsky GA. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics* **2010**;125:e35-e51.
15. Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective. *Int J Pediatr* **2014**;2014:571609.
16. Li Y, Migueles SA, Welcher B, Svehla K, Phogat A, Louder MK, Wu X, Shaw GM, Connors M, Wyatt RT, Mascola JR. Broad HIV-1 neutralization mediated by CD4-binding site antibodies. *Nat Med* **2007**;13:1032-4.
17. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarragona-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee DA, Manigart O, Karita E, Inwoley A, Jaoko W, Dehovitz J, Bekker LG, Pitisuttithum P, Paris R, Walker LM, Pognard P, Wrin T, Fast PE, Burton DR, Koff WC. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. *J Virol* **2009**;83:7337-48.
18. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, McKee K, O'Dell S, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science* **2010**;329:856-61.
19. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, Kwon YD, Scheid JF, Shi W, Xu L, Yang Y, Zhu J, Nussenzweig MC, Sodroski J, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science* **2010**;329:811-7.
20. Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, Wibmer CK, Puren A, DeCamp A, Gilbert PB, Wood B, Montefiori DC, Binley JM, Shaw GM, Haynes BF, Mascola JR, Morris L. Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. *J Virol* **2009**;83:8925-37.
21. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol* **2011**;85:4828-40.
22. Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez BM, Silacci C, Pinna D, Jarrossay D, Balla-Jhaghoorsingh S, Willems B, Zekveld MJ, Dreja H, O'Sullivan E, Pade C, Orkin C, Jeffs SA, Montefiori DC, Davis D, Weissenhorn W, McKnight A, Heeney JL, Sallusto F, Sattentau QJ, Weiss RA, Lanzavecchia A. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. *PLoS ONE* **2010**;5:e8805.

23. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, Wang SK, Ramos A, Chan-Hui PY, Moyle M, Mitcham JL, Hammond PW, Olsen OA, Phung P, Fling S, Wong CH, Phogat S, Wrin T, Simek MD, Koff WC, Wilson IA, Burton DR, Poignard P. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* **2011**;477:466-70.
24. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, Pietzsch J, Fenyo D, Abadir A, Velinzon K, Hurley A, Myung S, Boulad F, Poignard P, Burton DR, Pereyra F, Ho DD, Walker BD, Seaman MS, Bjorkman PJ, Chait BT, Nussenzweig MC. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science* **2011**;333:1633-7.
25. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, Wood B, Nathe C, Richman D, Tomaras GD, Bibollet-Ruche F, Robinson JE, Morris L, Shaw GM, Montefiori DC, Mascola JR. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. *J Virol* **2008**;82:11651-68.
26. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, Stamatatos L. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. *J Virol* **2009**;83:757-69.
27. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, Wu X, Seaman MS, Wrin T, Kwong PD, Wyatt RT, Mascola JR, Poignard P, Burton DR. PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. *J Virol* **2012**;86:4394-403.
28. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL, Lehrman JK, Priddy FH, Olsen OA, Frey SM, Hammond PW, Kaminsky S, Zamb T, Moyle M, Koff WC, Poignard P, Burton DR. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science* **2009**;326:285-9.
29. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, Phogat SK, Poignard P, Burton DR. A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. *PLoS Pathog* **2010**;6:e1001028.
30. McLellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, Louder R, Pejchal R, Sastry M, Dai K, O'Dell S, Patel N, Shahzad-ul-Hussan S, Yang Y, Zhang B, Zhou T, Zhu J, Boyington JC, Chuang GY, Diwanji D, Georgiev I, Kwon YD, Lee D, Louder MK, Moquin S, Schmidt SD, Yang ZY, Bonsignori M, Crump JA, Kapiga SH, Sam NE, Haynes BF, Burton DR, Koff WC, Walker LM, Phogat S, Wyatt R, Orwenyo J, Wang LX, Arthos J, Bewley CA, Mascola JR, Nabel GJ, Schief WR, Ward AB, Wilson IA, Kwong PD. Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature* **2011**;480:336-43.
31. Kong L, Lee JH, Doores KJ, Murin CD, Julien JP, McBride R, Liu Y, Marozsan A, Cupo A, Klasse PJ, Hoffenberg S, Caulfield M, King CR, Hua Y, Le KM, Khayat R, Deller MC, Clayton T, Tien H, Feizi T, Sanders RW, Paulson JC, Moore JP, Stanfield RL,

- Burton DR, Ward AB, Wilson IA. Supersite of immune vulnerability on the glycosylated face of HIV-1 envelope glycoprotein gp120. *Nat Struct Mol Biol* **2013**;20:796-803.
32. Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, Imamichi H, Bailer RT, Chakrabarti B, Sharma SK, Alam SM, Wang T, Yang Y, Zhang B, Migueles SA, Wyatt R, Haynes BF, Kwong PD, Mascola JR, Connors M. Broad and potent neutralization of HIV-1 by a gp41-specific human antibody. *Nature* **2012**;491:406-12.
33. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat Med* **2009**;15:866-70.
34. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. *Curr Opin Immunol* **2010**;22:358-66.
35. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, Kaufmann DE, McElrath MJ, Nussenzweig MC, Pulendran B, Scanlan CN, Schief WR, Silvestri G, Streeck H, Walker BD, Walker LM, Ward AB, Wilson IA, Wyatt R. A Blueprint for HIV Vaccine Discovery. *Cell Host Microbe* **2012**;12:396-407.
36. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. *Proc Natl Acad Sci U S A* **2005**;102:14943-8.
37. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **2012**;37:412-25.
38. Georgiev IS, Gordon JM, Zhou T, Kwong PD. Elicitation of HIV-1-neutralizing antibodies against the CD4-binding site. *Curr Opin HIV AIDS* **2013**;8:382-92.
39. Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, Imamichi H, Doria-Rose N, Hoxie JA, Connors M, Shaw GM, Wyatt RT, Mascola JR. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol* **2012**;86:5844-56.
40. Shibata R, Igarashi T, Haigwood N, Buckler-White A, Ogert R, Ross W, Willey R, Cho MW, Martin MA. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat Med* **1999**;5:204-10.
41. Baba TW, Liska V, Hofmann-Lehmann R, Vlasak J, Xu W, Ayehunie S, Cavacini LA, Posner MR, Katinger H, Stiegler G, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Lu Y, Wright JE, Chou TC, Ruprecht RM. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat Med* **2000**;6:200-6.
42. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Jiang S, Li PL, Baba TW, Montefiori DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Ruprecht RM. Postnatal pre- and postexposure passive immunization strategies: protection of neonatal macaques against oral simian-human immunodeficiency virus challenge. *J Med Primatol* **2002**;31:109-19.

43. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
44. Hessel AJ, Rakasz EG, Poignard P, Hangartner L, Landucci G, Forthal DN, Koff WC, Watkins DI, Burton DR. Broadly neutralizing human anti-HIV antibody 2G12 is effective in protection against mucosal SHIV challenge even at low serum neutralizing titers. *PLoS Pathog* **2009**;5:e1000433.
45. Hessel AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nat Med* **2009**;15:951-4.
46. Moldt B, Rakasz EG, Schultz N, Chan-Hui PY, Swiderek K, Weisgrau KL, Piaskowski SM, Bergman Z, Watkins DI, Poignard P, Burton DR. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. *Proc Natl Acad Sci U S A* **2012**;109:18921-5.
47. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, McKee K, Kong WP, Shi W, Chen X, Todd JP, Letvin NL, Huang J, Nason MC, Hoxie JA, Kwong PD, Connors M, Rao SS, Mascola JR, Nabel GJ. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. *Sci Transl Med* **2014**;6:243ra88.
48. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, Zeng M, Schmidt SD, Todd JP, Penzak SR, Saunders KO, Nason MC, Haase AT, Rao SS, Blumberg RS, Mascola JR, Nabel GJ. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature* **2014**;514:642-5.
49. Rudicell RS, Kwon YD, Ko SY, Pegu A, Louder MK, Georgiev IS, Wu X, Zhu J, Boyington JC, Chen X, Shi W, Yang ZY, Doria-Rose NA, McKee K, O'Dell S, Schmidt SD, Chuang GY, Druz A, Soto C, Yang Y, Zhang B, Zhou T, Todd JP, Lloyd KE, Eudailey J, Roberts KE, Donald BR, Bailer RT, Ledgerwood J, Mullikin JC, Shapiro L, Koup RA, Graham BS, Nason MC, Connors M, Haynes BF, Rao SS, Roederer M, Kwong PD, Mascola JR, Nabel GJ. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* **2014**;88:12669-82.
50. Florese RH, Demberg T, Xiao P, Kuller L, Larsen K, Summers LE, Venzon D, Cafaro A, Ensoli B, Robert-Guroff M. Contribution of nonneutralizing vaccine-elicited antibody activities to improved protective efficacy in rhesus macaques immunized with Tat/Env compared with multigenic vaccines. *J Immunol* **2009**;182:3718-27.
51. Forthal DN, Landucci G, Phan TB, Becerra J. Interactions between natural killer cells and antibody Fc result in enhanced antibody neutralization of human immunodeficiency virus type 1. *J Virol* **2005**;79:2042-9.
52. Asmal M, Sun Y, Lane S, Yeh W, Schmidt SD, Mascola JR, Letvin NL. Antibody-dependent cell-mediated viral inhibition emerges after simian immunodeficiency virus

SIVmac251 infection of rhesus monkeys coincident with gp140-binding antibodies and is effective against neutralization-resistant viruses. *J Virol* **2011**;85:5465-75.

53. Tudor D, Derrien M, Diomedea L, Drillet AS, Houimel M, Moog C, Reynes JM, Lopalco L, Bomsel M. HIV-1 gp41-specific monoclonal mucosal IgAs derived from highly exposed but IgG-seronegative individuals block HIV-1 epithelial transcytosis and neutralize CD4(+) cell infection: an IgA gene and functional analysis. *Mucosal Immunol* **2009**;2:412-26.
54. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, Shapiro L, Mascola JR. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature* **2014**;509:55-62.
55. Pancera M, Shahzad-ul-Hussan S, Doria-Rose NA, McLellan JS, Bailer RT, Dai K, Loesgen S, Louder MK, Staupe RP, Yang Y, Zhang B, Parks R, Eudailey J, Lloyd KE, Blinn J, Alam SM, Haynes BF, Amin MN, Wang LX, Burton DR, Koff WC, Nabel GJ, Mascola JR, Bewley CA, Kwong PD. Structural basis for diverse N-glycan recognition by HIV-1-neutralizing V1-V2-directed antibody PG16. *Nat Struct Mol Biol* **2013**;20:804-13.
56. Zhou T, Lynch RM, Chen L, Acharya P, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, McKee K, O'Dell S, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, Peng HP, Yang AS, Mullikin JC, Gray MD, Stamatatos L, Burton DR, Koff WC, Cohen MS, Haynes BF, Casazza JP, Connors M, Corti D, Lanzavecchia A, Sattentau QJ, Weiss RA, West AP, Jr., Bjorkman PJ, Scheid JF, Nussenzweig MC, Shapiro L, Mascola JR, Kwong PD. Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors. *Cell* **2015**;161:1280-92.
57. Chuang GY, Acharya P, Schmidt SD, Yang Y, Louder MK, Zhou T, Kwon YD, Pancera M, Bailer RT, Doria-Rose NA, Nussenzweig MC, Mascola JR, Kwong PD, Georgiev IS. Residue-level prediction of HIV-1 antibody epitopes based on neutralization of diverse viral strains. *J Virol* **2013**;87:10047-58.
58. Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, Denham SA, Heil ML, Kasolo F, Musonda R, Hahn BH, Shaw GM, Korber BT, Allen S, Hunter E. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* **2004**;303:2019-22.
59. Wilen CB, Parrish NF, Pfaff JM, Decker JM, Henning EA, Haim H, Petersen JE, Wojcechowskyj JA, Sodroski J, Haynes BF, Montefiori DC, Tilton JC, Shaw GM, Hahn BH, Doms RW. Phenotypic and immunologic comparison of clade B transmitted/founder and chronic HIV-1 envelope glycoproteins. *J Virol* **2011**;85:8514-27.

60. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, Karon J, Brookmeyer R, Kaplan EH, McKenna MT, Janssen RS. Estimation of HIV incidence in the United States. *JAMA* **2008**;300:520-9.
61. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, Lin LS, An Q, Mermin J, Lansky A, Hall HI. Estimated HIV incidence in the United States, 2006-2009. *PLoS ONE* **2011**;6:e17502.
62. Centers for Disease Control and Prevention. Diagnosis of HIV infection in the United States and dependent areas, 2013. HIV Surveillance Report, 2013; Vol. 25. <http://www.cdc.gov/hiv/library/reports/surveillance/>. 2015. Last accessed: 5-13-2015
63. Centers for Disease Control and Prevention. Estimates HIV incidence in the United States, 2007-2010. HIV Surveillance Supplemental Report 2012:17(No. 4). <http://www.cdc.gov/hiv/library/reports/surveillance/index.html>. 12-2-2015. Last accessed: 5-13-2015
64. Koblin BA, Mayer KH, Eshleman SH, Wang L, Mannheimer S, Del RC, Shoptaw S, Magnus M, Buchbinder S, Wilton L, Liu TY, Cummings V, Piwowar-Manning E, Fields SD, Griffith S, Elharrar V, Wheeler D. Correlates of HIV acquisition in a cohort of Black men who have sex with men in the United States: HIV prevention trials network (HPTN) 061. *PLoS ONE* **2013**;8:e70413.
65. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, Salazar LF, Frew P, Wingood G, Diclemente R, Del RC, Mulligan M, Sanchez TH. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. *PLoS ONE* **2014**;9:e90514.
66. World Medical Association. Ethical Principles for Medical Research Involving Human Subjects, Note of Clarification on Paragraph 29. **2002**.
67. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* **2000**;283:2701-11.
68. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. *N Engl J Med* **2001**;345:915-9.
69. Ng CT, Jaworski JP, Jayaraman P, Sutton WF, Delio P, Kuller L, Anderson D, Landucci G, Richardson BA, Burton DR, Forthal DN, Haigwood NL. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. *Nat Med* **2010**;16:1117-9.
70. Lynch RM, Wong P, Tran L, O'Dell S, Nason MC, Li Y, Wu X, Mascola JR. HIV-1 fitness cost associated with escape from the VRC01 class of CD4 binding site neutralizing antibodies. *J Virol* **2015**;89:4201-13.
71. Gilbert PB, Grove D, Gabriel E, Huang Y, Gray G, Hammer SM, Buchbinder SP, Kublin J, Corey L, Self SG. A Sequential Phase 2b Trial Design for Evaluating Vaccine Efficacy and Immune Correlates for Multiple HIV Vaccine Regimens. *Stat Commun Infect Dis* **2011**;3.

72. Kamb ML, Fishbein M, Douglas JM, Jr., Rhodes F, Rogers J, Bolan G, Zenilman J, Hoxworth T, Malotte CK, Iatesta M, Kent C, Lentz A, Graziano S, Byers RH, Peterman TA. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA* **1998**;280:1161-7.
73. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* **2014**;14:820-9.
74. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, Nardone A, Fisher M, McOwan A, Phillips AN, Johnson AM, Gazzard B, Gill ON. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* **2015**.
75. McCormack S, Dunn D. Pragmatic open-label randomized trial of preexposure prophylaxis: The PROUD study (Abstract 22LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
76. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On demand PrEP with Oral TDF-FTC in MSM: Results of the ANRS Ipergay trial (Abstract 23LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
77. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaunerie C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Preau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Dore V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* **2015**;373:2237-46.
78. Centers for Disease Control and Prevention. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex With Men. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm>. 1-28-2011. Last accessed: 4-10-2015
79. World Health Organization. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. July 2012. **2012**.
80. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: A Clinical Practice Guideline. **2014**.
81. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: Clinical Providers' Supplement. 2014. US Centers for Disease Control and Prevention.

82. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>. 6-30-2013. Last accessed: 2-2-2015
83. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. **2015**.
84. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, Chege W, Postle BS, Matheson T, Amico KR, Liegler T, Rawlings MK, Trainor N, Blue RW, Estrada Y, Coleman ME, Cardenas G, Feaster DJ, Grant R, Philip SS, Elion R, Buchbinder S, Kolber MA. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. *JAMA Intern Med* **2015**;1-11.
85. Hoagland B, Veloso V, De Boni R, Madruga J, Kallas E, Fernandes N, Moreira R, Liu A, Grinsztejn B, PrEP Brasil Study Team. Pre-exposure prophylaxis (PrEP) uptake and associated factors among MSM and TGW in the PrEP Brasil demonstration project (TUAC0205LB) . IAS 2015, 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2015, Vancouver, Canada, **2015**
86. Dawson L, Garner S, Anude C, Ndebele P, Karuna S, Holt R, Broder G, Handibode J, Hammer SM, Sobieszczyk ME. Testing the waters: Ethical considerations for including PrEP in a phase IIb HIV vaccine efficacy trial. *Clin Trials* **2015**;12:394-402.
87. Fuchs JD, Sobieszczyk ME, Madenwald T, Grove D, Karuna ST, Andrasik M, Sherwat A, Broder G, Mayer K, Koblin B, Hammer S. Intentions to Use Preexposure Prophylaxis Among Current Phase 2B Preventive HIV-1 Vaccine Efficacy Trial Participants. *J Acquir Immune Defic Syndr* **2013**;63:259-62.
88. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, Hare CB. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clin Infect Dis* **2015**;61:1601-3.
89. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, Gupta S, Herzyk D, Hurst C, Ivens IA, Kawabata T, Maier C, Mounho B, Rup B, Shankar G, Smith H, Thomas P, Wierda D. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol* **2009**;54:164-82.
90. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* **2004**;93:2645-68.
91. Li Y, O'Dell S, Walker LM, Wu X, Guenaga J, Feng Y, Schmidt SD, McKee K, Louder MK, Ledgerwood JE, Graham BS, Haynes BF, Burton DR, Wyatt RT, Mascola JR. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *J Virol* **2011**;85:8954-67.
92. Haynes BF, Fleming J, St Clair EW, Katinger H, Stiegler G, Kunert R, Robinson J, Searce RM, Plonk K, Staats HF, Ortel TL, Liao HX, Alam SM. Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* **2005**;308:1906-8.

93. Mascola JR, Lewis MG, Stiegler G, Harris D, VanCott TC, Hayes D, Louder MK, Brown CR, Sapan CV, Frankel SS, Lu Y, Robb ML, Katinger H, Birx DL. Protection of Macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol* **1999**;73:4009-18.
94. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, Beary H, Hayes D, Frankel SS, Birx DL, Lewis MG. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat Med* **2000**;6:207-10.
95. Mascola JR. Defining the protective antibody response for HIV-1. *Curr Mol Med* **2003**;3:209-16.
96. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
97. Parren PW, Marx PA, Hessel AJ, Luckay A, Harouse J, Cheng-Mayer C, Moore JP, Burton DR. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* **2001**;75:8340-7.
98. Sadjadpour R, Donau OK, Shingai M, Buckler-White A, Kao S, Strebel K, Nishimura Y, Martin MA. Emergence of gp120 V3 variants confers neutralization resistance in an R5 simian-human immunodeficiency virus-infected macaque elite neutralizer that targets the N332 glycan of the human immunodeficiency virus type 1 envelope glycoprotein. *J Virol* **2013**;87:8798-804.
99. Gautam R, Nishimura Y, Lee WR, Donau O, Buckler-White A, Shingai M, Sadjadpour R, Schmidt SD, LaBranche CC, Keele BF, Montefiori D, Mascola JR, Martin MA. Pathogenicity and mucosal transmissibility of the R5-tropic simian/human immunodeficiency virus SHIV(AD8) in rhesus macaques: implications for use in vaccine studies. *J Virol* **2012**;86:8516-26.
100. Shingai M, Donau OK, Plishka RJ, Buckler-White A, Mascola JR, Nabel GJ, Nason MC, Montefiori D, Moldt B, Pognard P, Diskin R, Bjorkman PJ, Eckhaus MA, Klein F, Mouquet H, Cetrulo Lorenzi JC, Gazumyan A, Burton DR, Nussenzweig MC, Martin MA, Nishimura Y. Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques. *J Exp Med* **2014**;211:2061-74.
101. Hessel AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. Fc receptor but not complement binding is important in antibody protection against HIV. *Nature* **2007**;449:101-4.
102. Saunders KO, Pegu A, Georgiev IS, Zeng M, Joyce MG, Yang ZY, Ko SY, Chen X, Schmidt SD, Haase AT, Todd JP, Bao S, Kwong PD, Rao SS, Mascola JR, Nabel GJ. Sustained Delivery of a Broadly Neutralizing Antibody in Nonhuman Primates Confers

Long-Term Protection against Simian/Human Immunodeficiency Virus Infection. *J Virol* **2015**;89:5895-903.

103. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, DeZure A, Lynch RM, Gordon I, Plummer S, Hendel CS, Pegu A, Conan-Cibotti M, Sitar S, Bailer RT, Narpala S, McDermott A, Louder M, O'Dell S, Mohan S, Pandey JP, Schwartz RM, Hu Z, Koup RA, Capparelli E, Mascola JR, Graham BS. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol* **2015**;182:289-301.
104. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* **2010**;9:325-38.
105. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol* **2009**;5:499-521.
106. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* **2010**;14:E10-E21.
107. World Health Organization. Policy Brief: Pre-exposure prophylaxis (PrEP): WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). **2015**.
108. Rosenbaum P. The consequences of adjustment for a concomitant variable that has been affected by the treatment. *Journal of the Royal Statistical Society, Series A (General)* **1984**;147:656-66.
109. Joffe MM, Greene T. Related causal frameworks for surrogate outcomes. *Biometrics* **2009**;65:530-8.
110. Follmann D. Augmented designs to assess immune response in vaccine trials. *Biometrics* **2006**;62:1161-9.
111. Gilbert PB, Hudgens MG. Evaluating candidate principal surrogate endpoints. *Biometrics* **2008**;64:1146-54.
112. Huang Y, Gilbert PB, Wolfson J. Design and estimation for evaluating principal surrogate markers in vaccine trials. *Biometrics* **2013**;69:301-9.
113. Rida W, Fast P, Hoff R, Fleming T. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol* **1997**;16:195-203.
114. Juraska, M, Grove, D, Yu, X, and Gilbert, PG. seqDesign: Simulation and Group Sequential Monitoring of Randomized Two-Stage Treatment Efficacy Trials with Time-to-Event Endpoints. R package version 1.1. <http://CRAN.R-project.org?package=seqDesign>. 4-27-2015. Last accessed: 5-15-2015
115. Berger RL, Boos DD. P values maximized over a confidence set for the nuisance parameter. *Journal of the American Statistical Association* **1994**;89:1012-6.

116. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials* **2010**;7:197-208.
117. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* **2013**;369:2083-92.
118. Fogel JM, Wang L, Parsons TL, Ou SS, Piwowar-Manning E, Chen Y, Mudhune VO, Hosseini pour MC, Kumwenda J, Hakim JG, Chariyalertsak S, Panchia R, Sanne I, Kumarasamy N, Grinsztejn B, Makhema J, Pilotto J, Santos BR, Mayer KH, McCauley M, Gamble T, Bumpus NN, Hendrix CW, Cohen MS, Eshleman SH. Undisclosed antiretroviral drug use in a multinational clinical trial (HIV Prevention Trials Network 052). *J Infect Dis* **2013**;208:1624-8.
119. Marzinke MA, Clarke W, Wang L, Cummings V, Liu TY, Piwowar-Manning E, Breaud A, Griffith S, Buchbinder S, Shoptaw S, Del RC, Magnus M, Mannheimer S, Fields SD, Mayer KH, Wheeler DP, Koblin BA, Eshleman SH, Fogel JM. Nondisclosure of HIV status in a clinical trial setting: antiretroviral drug screening can help distinguish between newly diagnosed and previously diagnosed HIV infection. *Clin Infect Dis* **2014**;58:117-20.
120. Chen I, Connor MB, Clarke W, Marzinke MA, Cummings V, Breaud A, Fogel JM, Laeyendecker O, Fields SD, Donnell D, Griffith S, Scott HM, Shoptaw S, Del RC, Magnus M, Mannheimer S, Wheeler DP, Mayer KH, Koblin BA, Eshleman SH. Antiretroviral Drug Use and HIV Drug Resistance Among HIV-Infected Black Men Who Have Sex With Men: HIV Prevention Trials Network 061. *J Acquir Immune Defic Syndr* **2015**;69:446-52.
121. Chen I, Clarke W, Ou S, Marzinke M, Breaud A, Hughes J, Richardson P, Haley D, Adimora A, Golin C, del Rio C, Kuo I, Mannhaimer S, Soto-Torres L, Rompalo A, Justman J, Hodder S, Eshleman S. Antiretroviral drug use in a cohort of HIV-uninfected women in the United States . 8th IAS Conference on HIV Pathogenesis, Treatment, and Prevention, Vancouver, Canada, July 19-22, **2015**
122. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data (Second Edition)*. John Wiley & Sons, Inc., **2002**.
123. Moore K, van der Laan M. Application of time-to-event methods in the assessment of safety in clinical trials. U. C. Berkeley Division of Biostatistics Working Paper Series, Paper 248. 2009.
124. van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. Springer, **2011**.
125. Gilbert PB, Wei LJ, Kosorok MR, Clemens JD. Simultaneous inferences on the contrast of two hazard functions with censored observations. *Biometrics* **2002**;58:773-80.
126. Edlefsen P, Magaret C, Poon A, Matsen I, Eller L, Tovanabutra S, Chopera D, Labuschagne P, Warth C, Holzman T, Rossenkahn R, Abrahams M-R, Logan M,

Anthony C, Botha G, Matten D, Nitayaphan S, Rono K, Sekiziyivu A, Ndabambi N, Travers S, Michael N, Williamson C, Robb N, Gilbert P. Systematic evaluation of HIV infection time and founder inferences using SGA and Illumina sequences . Keystone Symposia on Molecular and Cellular Biology, HIV Vaccines (X8), Olympic Valley, California, USA, March 20-24, 2016, **2016**

127. Crooks GE, Hon G, Chandonia JM, Brenner SE. WebLogo: a sequence logo generator. *Genome Res* **2004**;14:1188-90.
128. Schneider TD, Stephens RM. Sequence logos: a new way to display consensus sequences. *Nucleic Acids Res* **1990**;18:6097-100.
129. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, Sinangil F, D'Souza P, Rodriguez-Chavez IR, DeCamp A, Giganti M, Berman PW, Self SG, Montefiori DC. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. *J Infect Dis* **2010**;202:595-605.
130. Montefiori DC. Measuring HIV neutralization in a luciferase reporter gene assay. *Methods Mol Biol* **2009**;485:395-405.
131. Todd CA, Greene KM, Yu X, Ozaki DA, Gao H, Huang Y, Wang M, Li G, Brown R, Wood B, D'Souza MP, Gilbert P, Montefiori DC, Sarzotti-Kelsoe M. Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells. *J Immunol Methods* **2012**;375:57-67.
132. Ozaki DA, Gao H, Todd CA, Greene KM, Montefiori DC, Sarzotti-Kelsoe M. International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials. *PLoS ONE* **2012**;7:e30963.
133. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodhi N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Masse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2015**;372:509-18.
134. UNAIDS. Ethical considerations in biomedical HIV prevention trials. **2007**.
135. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. **1979**.
136. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. *Bull Med Ethics* **2002**;17-23.
137. UNAIDS/JC1853E (Second edition J2. Good participatory practice: Guidelines for biomedical HIV prevention trials. 2011.

Appendix A Sample informed consent form

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test the antibody called VRC01 against HIV. HIV is the virus that causes AIDS. Antibodies are one of the natural ways the body fights infection. Researchers can also make antibodies in laboratories and give them to people intravenously (with an IV). We will tell you more about this procedure below. This has been done successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 2700 people will take part in this study at multiple sites in North and South America. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

In addition, a similar study will be done with 1500 women in sub-Saharan Africa.

1. We are doing this study to answer several questions.

- Is the antibody safe to give to people?
- Are people able to take the antibody without becoming too uncomfortable?
- Does the antibody lower people's chances of getting infected with HIV?
- If the antibody does lower people's chances of getting infected with HIV, how much of it is needed to provide protection from HIV?

2. The antibody cannot give you HIV.

It is impossible for the antibody to give you HIV. Also, it cannot cause you to give HIV to someone else. However, we do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. The antibody is experimental.

The antibody being tested is called VRC-HIVMAB060-00-AB. It is an antibody against the HIV virus. From here on, we will call it VRC01 or the antibody. It is an experimental product. That means we do not know whether the antibody will be safe to use in people, or whether it will work to prevent HIV infection. This antibody is used only in research studies.

VRC01 was developed by the Vaccine Research Center at the US National Institutes of Health (NIH).

In laboratory and animal studies, VRC01 attached to and prevented infection by many strains of HIV viruses from around the world. We do not know if the antibody will prevent HIV infection when given to people. This study is designed to help us answer that question.

Risks of VRC01 antibody:

There have been 3 studies using the antibody in people in the United States at the NIH Clinical Center and at HVTN clinics. As of October 2015, 139 people received the antibody or placebo (a liquid with no antibody in it). The antibody has been tested in one study with HIV-positive people and in 2 studies with HIV-negative people. So far, it has not made them too uncomfortable or caused serious health problems. After receiving the antibody, most people said that they felt mild pain, itching, and redness where the antibody was given to them. Of these people, some said they felt like they had the flu after getting the antibody, but that this feeling lasted a few hours at most.

One participant had chest discomfort and one had a rash. These participants might have gotten the antibody or the placebo. To be safe, no more antibody or placebo was given to these participants. Some participants have had mild body discomfort, muscle pain, or joint pain after getting the VRC01 antibody.

VRC01 may have other side effects that we do not know about yet.

General risks of antibodies:

Antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain.

Rarely, some antibodies have caused serious reactions. These reactions may be life-threatening. Please tell us if you have ever had any of the following reactions.

- One type of serious reaction, called anaphylaxis, may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face.

- A second type of serious reaction, called serum sickness, may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath.

Rarely, antibodies licensed for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with the VRC01 antibody.

When antibodies are given to a person by IV they do not last in the body more than a few months. Any antibody given to you in this study should be gone from your body several months after your last dose.

Joining the study

4. It is completely up to you whether or not to join the study.

Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

If you join this study, you may not be allowed to join some other kinds of HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Also during the study, you should not donate blood or tissue.

If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. If you want to join the study, we will screen you to see if you are eligible.

Screening involves a physical exam, HIV test and health history. A physical exam may include, but is not limited to:

- Checking your weight, temperature and blood pressure
- Looking in your mouth and throat
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also ask you about medications you are taking. We will ask you about behaviors that might put

you at risk for getting HIV. If you could become pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

(Sites: adapt the following section so it is applicable to the care available at your site)

6. If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.

- For the care that we cannot give, we will explain how we will help you get care elsewhere.

For health problems that are unrelated to the study, we will not pay for care.

7. If you could become pregnant, you must agree to use birth control to join this study.

Site: If you want to include Appendix B, Approved birth control methods for transgender men (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the antibody could affect the developing baby. You must agree to use effective birth control from 21 days before you first receive the antibody until your last scheduled clinic visit (about 1¾ years after your first IV). We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. You will come to the clinic for scheduled visits about [#] times over [#] months.

The study will require [#] visits. That is 1 visit every 4 weeks. You may have to come for more visits if you have a lab or health issue.

Visits can last from about [#] minutes to [#] hours. The IV procedure takes about 30 to 60 minutes.

We may contact you after the main study ends (for example, to tell you about the study results).

9. We will give you [Site: Insert compensation] for each study visit you complete.

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, birth control costs for participants capable of becoming pregnant).

Following paragraph for US sites only:

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

You do not have to pay anything to be in this study.

10. We will give you either the antibody or a placebo.

Not everyone in this study will get the VRC01 antibody. Some people will get a placebo, a liquid that does not contain any antibody. We will compare the results from people who got the placebo with results from people who got the VRC01 antibody. In this study, the placebo is sterile salt water, which is found naturally in the body.

There are three groups in this study. One group will get a lower dose of the VRC01 antibody, one group will get a higher dose, and one group will get the placebo. The high and low doses of the antibody will be adjusted for your body weight. We will weigh you to determine the amount you will get.

Overall, if you join this study, you have a 2-in-3 chance of getting the study antibody.

Site: Modify the randomization metaphor in the next sentence as appropriate to your local culture.

Whether you get the low dose of the antibody, the high dose of the antibody, or the placebo is completely random, like flipping a coin.

We have no say in whether you get the antibody or the placebo. If you get the antibody, we have no say in which dose you get. We will not know what you are getting, and neither will you. Only the pharmacist at this clinic will have this information while the study is going on.

You will have to wait until everyone completes their final study visits to find out whether you got the antibody or the placebo. This could be up to about 5 years. But, if you have a serious medical problem and need to know what you got before the end of the study, we can tell you.

If it is found to be effective, there are no plans to give the antibody to participants after the study. Instead, we will use what is learned in this study to determine if the antibody would be useful to prevent HIV, how the antibody could be improved, and how to produce it for wide public use.

11. We will give you the antibody or placebo on a schedule.

You will get the VRC01 antibody or the placebo during the study by IV. To get an IV, a needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small bag of fluid that contains the antibody or placebo. An IV pump controls how fast the fluid drips from the bag, through the tube, and into your vein. There will be 10 IV procedures, one IV every 8 weeks. Other study visits will not include IVs.

Infusion schedule



Group	Dose	First IV	Weeks after first IV								
			Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72
Group 1	Lower dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 2	Higher dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 3	Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

You will have to wait in the clinic for about 30 minutes after the first IV to see if there are any problems. You probably will not have to wait after the IVs at the rest of the IV visits. After each IV visit, for that night and for three more days, you will be asked to keep track of how you feel. To help you do this, we can give you tools and show you how to use them. We will ask you the ways we can contact you. We will contact you about 3 days after each IV visit to ask how you have been feeling. Contact the clinic staff if you have any concerns after getting an infusion. If you have a problem, we will continue to check on you until it goes away

12. In addition to giving you the antibody or placebo, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you could become pregnant;
- Ask questions about your health, including medications you may be taking;
- Ask questions about any personal problems or benefits you may have from being in the study; and
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 160 mL (2 teaspoons to $\frac{2}{3}$ cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, “To compare, people who donate blood in the US can give a total of about 500 mL in an 8-week period.”). Modify the example for cultural relevance and alter blood volumes as necessary.

Site: Insert Appendix D, Table of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

We will be looking for side effects.

We will do blood tests for syphilis and urine tests for gonorrhea and chlamydia. We will also test for gonorrhea and chlamydia using rectal swabs. We will do these tests at 4 visits. We will also test for gonorrhea and chlamydia using mouth and throat swabs at your first infusion visit. We will explain what each of these infections is. If the tests show that you have an infection, we will provide counseling and will help you get treatment. This study cannot pay for that treatment. *[Site: Revise preceding sentence if you provide or pay for STI treatment.]*

We will review the results of the procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. We will test your samples for this study.

We will send your samples (without your name) to labs approved by the HVTN and the HPTN for this study. These labs are located in the United States, South America, and South Africa. The samples will be tested to:

- measure how much antibody is in your blood,
- see how your immune system responds to the antibody, and
- see if there is antiretroviral medicine (also called ART/ARV) in your blood.

Researchers may also do genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The differences in people's genes can help explain why some people get a disease while others do not. These types of genetic tests involve only some of your genes, not all of your genes (your genome). The researchers will study the genes related to the immune system and HIV and those that affect how people get HIV.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the antibody.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

Tests done on your samples are for research purposes only. The labs will not give the results to you or this clinic, and the results will not become part of your study record.

When your samples are no longer needed for this study, the HVTN will continue to store them.

Site: Delete next section if using separate consent for use of samples and information in other studies

14. When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This section gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

Do I have to agree? No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

Where are the samples stored? Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

How long will the samples be stored? There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

Will I benefit from allowing my samples to be used in other studies? Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

How do other researchers get my samples and information? When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher’s location.

What information is shared with other researchers? The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

15. We will counsel you on reducing your risk for HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior and drug use. We will provide you with condoms and lubricant. We will talk with you about ways of lowering your risk of getting HIV. We will help you develop a risk reduction plan. Some topics we may discuss include:

- What you think causes risky behavior for you, and
- Ways to avoid getting HIV or giving it to someone else

[Site: adjust the language in this paragraph about PrEP provision to meet local availability.] These methods may include not having sex, using condoms, or other behavior changes. We will talk about new methods of HIV prevention, including pre-exposure prophylaxis (PrEP) with a drug called Truvada, and help you decide which of these methods is right for you.

[Site: The text in the next two paragraphs applies to US sites only. Sites should adjust the language in this paragraph to meet local PrEP availability.] Gilead Sciences, Inc. (the maker of Truvada) has agreed to provide Truvada as PrEP to study participants in HVTN 704/HPTN 085 through a mail order pharmacy. If you are interested, we can give you more information about this program. We can refer you to health care providers who can prescribe PrEP either through the Gilead program or from a different source.

If you accept the Gilead Sciences, Inc. offer to receive Truvada as PrEP during the study, the following study data will be shared with Gilead Sciences, Inc.:

- Your study ID code number
- Information such as your age, sex at birth, and gender
- Your past and present health conditions

Truvada has been shown to substantially lower people's risk of getting HIV when taken every day. The US FDA has approved it for use as PrEP in adults at risk of HIV infection through sexual contact. There are several considerations to talk about with your health care provider to see if PrEP is the right choice for you. If you decide to take Truvada PrEP, your health care provider will prescribe it for you and monitor your health while you use it.

[Site: The text in the next two paragraphs applies to South American sites only. Sites should adjust the language in this paragraph to meet local PrEP availability.] Gilead Sciences, Inc. (the maker of Truvada) has agreed to provide Truvada as PrEP to study participants in HVTN 704/HPTN 085 through a local project. If you are interested, clinic staff can give you more information about this project and can refer you to it for PrEP.

PrEP has been shown to lower people's risk of getting HIV when taken once every day. There are several medical considerations to talk about with health care providers at the project to see if PrEP is the right choice for you. A provider at the project will prescribe PrEP for you and monitor your health while you use it.

In this study, we will look at how many participants use PrEP. We will also try to find out if using PrEP has any effect on how VRC01 works.

16. If you are HIV infected when you enroll or become infected during the study, we will help you get care and support.

We will test your blood for HIV before your first IV and during the study. Each time, it will take a few days to complete the tests. If you are infected with HIV, you cannot stay in the study for its whole length. If that happens, we will tell you as soon as possible. We will also ask you to come to the clinic for 3-6 more visits. We will tell you more about what will happen at these visits in another form.

17. We may stop your IVs or take you out of the study at any time. We may do this even if you want to stay in the study and even if you were scheduled for more IVs.

This may happen if:

- you are unable to follow instructions,
- we think that staying in the study might harm you,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

If we stop your IVs, we may ask you to stay in the study to complete other study procedures.

18. If you stop getting IVs for reasons other than HIV infection, we will encourage you to stay in the study.

We will ask you to come in for study visits about every 3 months until 92 weeks after your first infusion. That is how long you would be in the study if you got all the infusions on schedule. Because you got some IVs, we want to keep track of your health. How many visits you will have will depend on when you stopped getting IVs. At these visits we will:

- Ask questions about your health, including medications you may be taking;
- Do physical exams based on your complaints or side effects;
- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Ask questions about any personal problems or benefits you may have from participating in the study;
- Do pregnancy tests if you could become pregnant; and
- Collect blood samples (between 70 mL and 120 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit).

19. We will stop your IVs if you become pregnant during the study.

We will encourage you to stay in the study if you choose. We will discuss your study options with you. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

20. We will do our best to protect your private information.

US sites: Check HIPAA authorization for conflicts with this section.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health, people who work for them, its study monitors, and its chosen South African representatives,
- The US Food and Drug Administration,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN and HPTN and people who work for them,
- The US National Institutes for Allergy and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.).

- [Item 1]
- [Item 2]
- [Item 3]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

Sites: The text below may not be deleted or changed, per FDA requirement. It's OK to remove the box around it.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At

most, the website will include a summary of the results. You can search this website at any time.

Other Risks

21. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of taking blood:

Taking blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of the IV procedures:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in infections.

Personal problems/discrimination:

Some people who join HVTN or HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry, get upset or angry, or assume that you are infected with HIV or at high risk and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

HIV testing

HIV antibody tests are the usual way to test for HIV infections. Although 2 out of 3 people in this study will get an HIV antibody, we do not expect them to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the VRC01 antibody and none of them detected the antibody.

Although it has not been seen so far, getting VRC01 may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

To be absolutely safe we ask you to get HIV tests only at this clinic during the study. Our tests can always detect true HIV infection. They can also tell if someone is really not HIV infected. Since the antibodies do not last long in the body, we do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you are

infected with HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

Risks of genetic testing:

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

U.S. Sites, include the following paragraph In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the antibody will increase, decrease, or not change your risk of becoming infected with HIV if exposed.

If we find that you were already HIV infected when you got the antibody, we do not know how the antibody will affect your HIV disease. We also do not know how having gotten it will affect your HIV-related lab results.

If you get infected with HIV during the study, we do not know how the antibody might affect the course of your HIV disease.

If you become pregnant while you still have VRC01 in your body, we don't know if it could be passed to your baby. We do not know how the antibody will affect a pregnant participant or a developing baby.

Benefits

22. The study may not benefit you.

Since we do not know if the antibody can prevent HIV infection in people, you should not expect any benefit from getting the antibody in this study. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

This study may show us that the VRC01 antibody can prevent HIV and the study results may also help in the search for methods to prevent HIV. However, if the VRC01 antibody later becomes approved and sold or leads to an HIV prevention method, there are no plans to share any money with you.

Your rights and responsibilities

23. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

24. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Injuries

Sites: Do not make changes to the following section without obtaining approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org.

25. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, there is a process to decide if it is related to the VRC01 antibody and/or study procedures. If it is, we call it a study-related injury.

The HVTN and HPTN have limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

26. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies.

27. In Section 14 of this form, we told you about possible other uses of your extra samples and limited information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

28. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.

- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix B Approved birth control methods for transgender men (for sample informed consent form)

You should not become pregnant during the study because we do not know how the study antibody could affect the developing baby.

If you were assigned female at birth and are sexually active in a way that could lead to pregnancy, you must agree to use effective birth control from 21 days before your first IV until your last scheduled clinic visit (about 1¾ years after your first IV). You should not become pregnant during the study because we do not know how the antibody could affect the developing baby.

Although taking testosterone can lower the chances of becoming pregnant, it is not considered an effective method of birth control. Effective birth control means using any of the following methods every time you have sex:

- Drugs that are prescribed specifically for birth control and intended to prevent pregnancy—these include pills, shots, patches, vaginal rings, or inserts under the skin;
- Male or female condoms, with or without a cream or gel that kills sperm;
- Diaphragm or cervical cap with a cream or gel that kills sperm;
- Intrauterine device (IUD); or
- Any other contraceptive method approved by the researchers.

You do not have to use birth control if:

- You have had a hysterectomy (your uterus removed);
- You have had an oophorectomy (your ovaries removed);
- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes; or
- You are sexually abstinent (no sex at all).

Appendix C Sample consent form for use of samples and information in other studies

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

HVTN protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

4. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

8. What information is shared with other researchers?

The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

U.S. Sites, include the following paragraph

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect

you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact [name and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact [name/title/phone of person on IRB or other appropriate organization].

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above and also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix D Tables of procedures (for sample informed consent form)

HIV-uninfected participants

Procedure	Screening visit(s)	First IV visit	6 months																1 year								1½ years							
			4 weeks	8 weeks	8 weeks + 5 days	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks	52 weeks	56 weeks	60 weeks	64 weeks	68 weeks	72 weeks	76 weeks	80 weeks	84 weeks	88 weeks	92 weeks								
IV		√		√			√		√		√		√		√		√		√		√													
Medical history	√																																	
Complete physical exam	√																																	√
Brief physical exam		√		√			√		√		√		√		√		√		√		√													
Urine test	√			√																													√	
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test*	√	√	√	√			√		√		√		√		√		√		√		√		√		√		√		√		√		√	
HIV test & pretest counseling	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Risk reduction counseling	√	√		√			√		√		√		√		√		√		√		√		√		√		√		√		√		√	
Interview/Questionnaire	√	√		√			√		√		√		√		√		√		√		√		√		√		√		√		√		√	
STI testing (blood, urine, and/or swabs) [†]		√							√						√						√													

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

[†] And if indicated by symptoms.

Participants who discontinue infusions for reasons other than HIV infection

Procedure	Weeks after enrollment							
	8	20	32	44	56	68	80	92
Brief physical (as needed)	√	√	√	√	√	√	√	
Complete physical								√
HIV testing & pretest counseling	√	√	√	√	√	√	√	√
Risk reduction counseling	√	√	√	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√	√	√	√
Pregnancy test*	√	√	√	√	√	√	√	√
Blood drawn	√	√	√	√	√	√	√	√

Study participants who discontinue infusions for reasons other than HIV infection will start this visit schedule at the first visit that occurs after their last infusion. Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Appendix E Sample consent form for participants with HIV infection at enrollment or during the study

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

Please read this consent form or ask someone to read it to you. If you decide to, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

You are a participant in a study called HVTN 704/HPTN 085, The AMP Study. The rest of the information in the consent form that you signed earlier, about the study purpose, the risks and benefits of participation, your rights and responsibilities, and how your privacy is protected, continues to be important information for you and has not changed.

About this form

We tested your blood for HIV and you were found to be infected. We will help you get care and support.

You became infected either prior to enrollment or during your participation in the study. Because of this, you cannot stay in the study for its whole length. We would like you to come to the clinic for a different number of visits than what is explained in the main study consent form.

Depending on when you became infected, you will come to the clinic for 2-5 more visits.

1. If you are found to have been HIV-1 infected when you enrolled, or if you have HIV-2 infection:

If you are found to have been HIV infected when you enrolled, you were already infected with HIV before you got the antibody or placebo. It takes a few days to complete the tests to see if you have HIV, so your infection was not found until after you got your first IV.

HIV-2 is a rare kind of HIV, most often found in West Africa. In North and South America, there are only about a dozen cases reported each year.

We will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s).

We are asking you to come to the clinic for 2 more visits over 6 months. At these visits, we will:

- Ask questions about your health;

- Do physical exams based on your complaints or side effects;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on how to reduce your risk and ways to avoid transmission;
- Collect blood samples (between 30 and 45 mL, or about 2 to 3 tablespoons, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

Site: You may remove the Table of procedures in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

Participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Weeks after 1 st positive HIV test	
	4	24
Medical history (as needed)	√	√
Brief physical (as needed)	√	√
Complete physical		√
Risk reduction counseling	√	√
Questions/questionnaire	√	√
Blood drawn	√	√

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

2. If you got infected with HIV-1 during the study:

If you became infected with HIV-1, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). You will not get any more IVs. We will ask you to come in for 5 additional visits over 6 months. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on how to reduce your risk and ways to avoid transmission;
- Collect blood samples (between 70 mL and 130 mL, about ⅓ to ½ cup, at each visit); and

- Ask questions about any personal problems or benefits you may have from participating in the study.

Site: You may remove the Table of procedures (for addendum consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

HIV-1–infected participants

Procedure	Weeks after 1 st positive HIV test				
	4	6	8	12	24
Medical history (as needed)	√	√	√	√	√
Brief physical (as needed)	√	√	√	√	
Complete physical					√
Risk reduction counseling	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√
Blood drawn	√	√	√	√	√
Pregnancy test*				√	

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected may be invited to join a separate study for follow-up visits. That study will have a separate schedule of visits and procedures. It will also have a separate consent form, which will be reviewed with all participants who are invited to join that study.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Leaving the study

Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Questions

If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

Your permissions and signature

If you agree to continue in this study with this new visit schedule, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand the changes to the visit schedule and what will happen to you. You understand that the possible risks and benefits of participation have not changed.
- You have had your questions answered and know that you can ask more at any time.
- You agree to continue in this study.

You will not be giving up any of your rights by signing this consent form.

_____	_____	_____	_____
Participant's name (print)	Participant's signature or mark	Date	Time
_____	_____	_____	_____
Study staff conducting consent discussion (print)	Study staff signature	Date	Time

For participants who are unable to read or write, also complete the signature block below:

_____	_____	_____	_____
Witness's name (print) [#]	Witness's signature	Date	Time

[#] Witness is impartial and was present for the consent process.

Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants

Visit: Day: Week:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total		
	Screening visit ¹	D0 W0	D28 W4	D56 W8	D61	D84 W12	D112 W16	D140 W20	D168 W24	D196 W28	D224 W32	D252 W36	D280 W40	D308 W44	D336 W48	D364 W52	D392 W56	D420 W60	D448 W64	D476 W68	D504 W72	D532 W76	D560 W80	D588 W84	D616 W88	D644 W92			
	Inf#1	Inf#2	Inf#3	Inf#4	Inf#5	Inf#6	Inf#7	Inf#8	Inf#9	Inf#10																			
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ⁴	Tube size (vol. capacity) ⁴																									
BLOOD COLLECTION																													
Screening/Diagnostic																													
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5		
HIV diagnostics ⁷	UW-VSL/ Regional Network HIV Dx Labs	UW-VSL/ Regional Network HIV Dx Labs	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20	260		
Safety labs																													
CBC/Differential	Local lab	Local lab	EDTA	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	55		
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	55		
STI Serology																													
Syphilis ¹¹	Local lab	Local lab	SST	5mL	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	5 ¹³	—	—	—	—	5 ¹³	—	—	—	—	20		
Drug Levels/Detection																													
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0		
ARV detection ¹⁰	CSR	JHU	SST	8.5mL	—	y	—	y	—	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	0		
Immunogenicity & Virologic Assays																													
Host genetics ⁵	CSR	FHCRC	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0		
Anti-VRC01 Ab levels	CSR	VRC/NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	y	—	—	—	—	—	—	—	—	y	—	—	—	0		
Functional humoral assays ⁸	CSR	Duke/SAIL-NICD/ VRC/NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0		
Viral isolation/sequencing ⁹	CSR	TBD	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	250		
STORAGE																													
Serum storage	CSR	—	SST	8.5mL	—	76.5	51	51	42.5	51	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	1139		
PBMC storage	CSR	—	ACD	8.5mL	—	51	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	34	153		
Visit total					15	163	71	81	63	71	73	63	78	63	73	71	107	63	78	63	73	63	112	71	63	63	107	1937	
56-Day total					15	178	249	330	215	286	287	206	213	203	213	206	250	240	247	203	213	198	208	198	247	245	245	196	232
URINE COLLECTION																													
Urine dipstick ¹⁵	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—		
Pregnancy Test ⁶	Local lab	Local lab			X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—		
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—		
RECTAL SWAB COLLECTION																													
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	—	—	—	—	X ¹³	—	—	—	—		
OROPHARYNGEAL SWAB COLLECTION																													
Gonorrhea ¹²	Local lab	Local lab			—	X ¹⁴	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		

¹ CSR = central specimen repository² HVTN Laboratory Program includes laboratories at UW-VSL, FHCRC, Duke, SAIL-NICD, and Regional Network HIV Diagnostic Laboratories. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); FHCRC = Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke = Duke University Medical Center (Durham, North Carolina, USA); SAIL-NICD = South African Immunology Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa).

Non-HVTN laboratory: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.⁴ Local labs may assign appropriate alternative tube types for locally performed tests.⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.⁶ For persons capable of becoming pregnant, pregnancy test must be performed on urine or blood specimens on the day of infusion with negative results received prior to infusion.⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.¹⁰ Testing plan for ARV detection to be determined.¹¹ Syphilis testing will be done by serology.¹² Chlamydia testing will be done with urine and rectal swabs. Gonorrhea testing will be done with urine, and rectal and oropharyngeal swabs.¹³ Syphilis testing, and chlamydia/gonorrhea testing by urine and rectal swab, will be performed at visits 2, 9, 15 and 21; in addition, testing may occur at any visit if indicated by symptoms.¹⁴ Gonorrhea testing by oropharyngeal swab will be performed at visit 2; in addition, testing may occur at any visit if indicated by symptoms.¹⁵ And microscopy if needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

TBD = To be determined

Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants

					Visit:	#.X ⁵	31	32	33	34	35	
					Days after diagnosis:	D14	D28	D42	D56	D84	D168	
					Weeks after diagnosis:	W2	W4	W6	W8	W12	W24	
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³								Total
BLOOD COLLECTION												
Screening or diagnostic assays												
HIV diagnostics ⁷	UW-VSL/ Regional Network HIV Dx Labs	UW-VSL/ Regional Network HIV Dx Labs	EDTA	10mL	20 ⁷	—	—	—	—	—	—	20
HIV PCR viral load	UW-VSL/ Regional Network HIV Dx Labs	UW-VSL/ Regional Network HIV Dx Labs	EDTA	10mL	—	10	10	10	10	10	10	50
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5	5	5	5	5	5	5	30
Safety lab												
Hemoglobin	Local Lab	Local Lab	EDTA	5mL	—	—	—	5	5	—	—	10
Drug levels												
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5	8.5	8.5	8.5	8.5	8.5	8.5	51
Immunogenicity & Virologic Assays												
Functional humoral assays ⁶	CSR	Duke/SAIL-NICD/ VRC/NVITAL	SST	8.5mL	17	17	17	17	17	17	17	102
Viral isolation/sequencing	CSR	TBD	EDTA	10mL	10	10	10	10	10	10	10	60
Storage												
Serum	CSR		SST	8.5mL	25.5	17	17	17	17	17	17	110.5
Plasma	CSR		EDTA	5mL	5	5	5	5	5	5	5	30
PBMC	CSR		ACD	8.5mL	34	—	—	—	34	34	34	102
Visit total					125	72.5	72.5	77.5	111.5	106.5	566	
56-Day total					125	198	270	348	334	106.5		
URINE COLLECTION												
Pregnancy Test ⁴	Local Lab	Local Lab			X	—	—	—	X	—	—	

¹ CSR = central specimen repository

² HVTN Laboratory Program includes laboratories at UW-VSL, Duke, SAIL-NICD, and Regional Network HIV Diagnostics Laboratories in South America. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Duke- Duke = Duke University Medical Center (Durham, North Carolina, USA); SAIL-NICD = South African Immunology, Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa).

Non-HVTN laboratory: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on blood specimens.

⁵ Confirmatory draw for HIV diagnostics will be collected at this visit.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ One tube will remain as a whole blood specimen and be shipped ambient to the HIV diagnostics laboratory; it should not be processed for plasma by the site-associated laboratory. The other tube will be processed for plasma as usual.

TBD = To be determined

Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

					Visit:	#.X	47	48	Total
					Days after diagnosis:	D14	D28	D168	
					Weeks after diagnosis:	W2	W4	W24	
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³					
BLOOD COLLECTION									
Screening or diagnostic assays									
HIV diagnostics ⁵	UW-VSL/ Regional Network HIV Dx Labs	UW-VSL/ Regional Network HIV Dx Labs	EDTA	10mL	20 ⁵	—	—	—	20
HIV PCR viral load	UW-VSL/ Regional Network HIV Dx Labs	UW-VSL/ Regional Network HIV Dx Labs	EDTA	10mL	—	10	10	10	20
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5	5	5	5	15
Storage									
Serum	CSR		SST	8.5mL	17	17	17	17	51
Visit total					42	32	32	32	106
56-Day total					42	74	32	32	
URINE COLLECTION									
Pregnancy Test ⁴	Local Lab	Local Lab			X	—	—	—	

¹ CSR = central specimen repository

² HVTN Laboratory Program includes laboratories at UW-VSL and Regional Network HIV Diagnostics Laboratories in South America. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on blood specimens.

⁵ One tube will remain as a whole blood specimen and be shipped ambient to the HIV diagnostics laboratory; it should not be processed for plasma by the site-associated laboratory. The other tube will be processed for plasma as usual.

Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection

					Visit:	71	72	73	74	75	76	77	78		
					Days after enrollment:	D56	D140	D224	D308	D392	D476	D560	D644		
					Weeks after enrollment:	W8	W20	W32	W44	W56	W68	W80	W92		

¹ CSR = central specimen repository

² HVTN Laboratory Program includes laboratories at UW-VSL, Duke, SAIL-NICD, and Regional Network HIV Diagnostics Laboratories in South America. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Duke = Duke University Medical Center (Durham, North Carolina, USA); SAIL-NICD = South African Immunology, Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa)..

Non-HVTN laboratory: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For participants capable of becoming pregnant; pregnancy test may be performed on blood specimens.

⁵ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 78 above.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ And microscopy if needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level and functional humoral assays; no separate blood draw is needed.

TBD = To be determined

Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants

Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Post
Day:	Screening	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D588	D616	D644	
Week:	visit ¹	W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	
Procedure	Scr.	Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10						
Study procedures²																											
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Risk reduction counseling	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Pregnancy prevention assessment ³	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Participant Questionnaire	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Concomitant medications	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Intercurrent illness/adverse experience	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
HIV infection assessment ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Local lab assessment																											
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine dipstick ¹²	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Pregnancy (urine or serum HCG) ⁵	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
CBC, differential	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
ALT, Creatinine	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Syphilis ⁶	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—
Chlamydia, Gonorrhea ⁸	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—
Study product administration procedures																											
IV infusion ¹⁰	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Reactogenicity assessment ¹¹	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Poststudy																											
Unblind participant	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

² For specimen collection requirements, see Appendix F.

³ Pregnancy prevention assessments are required only for participants who are capable of becoming pregnant.

⁴ Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

⁵ For a participant capable of becoming pregnant, pregnancy test must be performed on the day of infusion prior to infusion. Pregnancy test to determine eligibility may be performed at screening, but must also be done on Day 0 prior to infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.

⁶ Syphilis testing will be done by serology.

⁷ Syphilis and Chlamydia/Gonorrhea testing will be performed at visits 2, 9 15, and 21; in addition, testing may occur at any visit or if indicated by symptoms.

⁸ Chlamydia/Gonorrhea testing will be done with urine and rectal swabs; oropharyngeal swabs will be collected for gonorrhea testing at visit 2; in addition, testing may occur at any visit if indicated by symptoms..

¹⁰ Blood draws required at infusion visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests must be drawn within the 3 days prior to infusion.

¹¹ Reactogenicity assessments performed for 3 days postinfusion (see Section 7.10).

¹² And microscopy if needed.

Appendix K Schedule 2—Procedures at CRS for HIV-1–infected participants

Visit Number:	#.X ¹	31	32	33	34	35
Days after diagnosis	D14	D28	D42	D56	D84	D168
Weeks after diagnosis:	2	4	6	8	12	24
Study procedures²						
Counseling on HIV-1 testing/diagnosis	X	X	—	—	—	—
Abbreviated physical exam ³	X	X	X	X	X	—
Complete physical exam ³	—	—	—	—	—	X
ART assessment	X	X	X	X	X	X
Concomitant medications	—	X	X	X	X	X
Intercurrent illness/adverse experience	—	X	X	X	X	X
Transmission risk reduction counseling	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	—	—	—	—	X
Social impact assessment	X	X	X	X	X	X
Local lab assessment²						
Pregnancy test ⁴	X	—	—	—	X	—
CD4+ T cell count	X	X	X	X	X	X
Hemoglobin	—	—	—	X	X	—

¹ Visit #.X = interim visit for the purpose of drawing samples for confirmatory HIV testing

² For specimen collection requirements, see Appendix G.

³ Includes assessment of HIV/AIDS-related conditions.

⁴ For participants capable of becoming pregnant.

Appendix L Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Visit Number:	#.X ¹	47	48
Days after diagnosis	D14	D28	D168
Weeks after diagnosis:	2	4	24
Study procedures²			
Counseling on HIV-1 testing/diagnosis	X	X	—
Abbreviated physical exam ³	X	X	—
Complete physical exam ³	—	—	X
ART assessment	X	X	X
Concomitant medications	—	X	X
Intercurrent illness/adverse experience	—	X	X
Transmission risk reduction counseling	X	X	X
Behavioral risk assessment questionnaire	—	—	X
Social impact assessment	X	X	X
Local lab assessment²			
Pregnancy test ⁴	X	—	—
CD4+ T cell count	X	X	X

¹ Visit #.X = interim visit for the purpose of drawing samples for confirmatory HIV testing

² For specimen collection requirements, see Appendix H.

³ Includes assessment of HIV/AIDS-related conditions.

⁴ For participants capable of becoming pregnant.

Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection

Visit Number:	71	72	73	74	75	76	77	78
Days after enrollment:	56	140	224	308	392	476	560	644
Weeks after enrollment:	8	20	32	44	56	68	80	92
Study procedures¹								
Abbreviated physical exam	X	X	X	X	X	X	X	—
Complete physical exam	—	—	—	—	—	—	—	X
Risk reduction counseling	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Intercurrent illness/adverse experience	X	X	X	X	X	X	X	X
HIV infection assessment ²	X	X	X	X	X	X	X	X
Confirm HIV test results provided to participant	X	X	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	X	—	X	—	X	—	X
Social impact assessment	X	X	X	X	X	X	X	X
Local lab assessment¹								
Urine dipstick ³	X	—	—	—	—	—	X	—
Pregnancy test ⁴	X	—	X	—	X	—	X	—

¹ For specimen collection requirements, see Appendix I.

² Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

³ And microscopy if needed.

⁴ For participants capable of becoming pregnant.



PROTOCOL

HVTN 704/HPTN 085

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

DAIDS DOCUMENT ID 30095

IND 113,611 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS
Bethesda, Maryland, USA

June 15, 2017
HVTN 704/HPTN 085
Version 3.0

Contents

1	Overview	5
1.1	Protocol Team.....	8
2	Background	11
2.1	Rationale for trial concept	11
2.2	bnAbs to HIV-1	12
2.3	VRC01: VRC-HIVMAB060-00-AB	14
2.4	Trial design rationale	15
2.5	Combination Prevention for HIV acquisition.....	20
2.6	Plans for future product development and testing	23
2.7	Preclinical safety studies.....	23
2.8	Nonhuman primate (NHP) studies of VRC01	26
2.9	Clinical trial experience.....	28
2.10	Potential risks of study products and administration	35
3	Objectives and endpoints	38
3.1	Primary objectives and endpoints	38
3.2	Secondary objectives and endpoints	38
3.3	Exploratory objectives	39
4	Statistical considerations.....	40
4.1	Outline of the statistical considerations section.....	40
4.2	PE parameter for the primary analysis of prevention efficacy	40
4.3	PE parameters for secondary analyses of prevention efficacy.....	41
4.4	Statistical rationale for the 3-arm design compared to a 2-arm design.....	42
4.5	Use of safety run-in data in the analyses of prevention efficacy	43
4.6	Sample size calculations for testing for overall PE (Primary objective 2) ..	43
4.7	Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group	51
4.8	Sample size calculations for safety	52
4.9	Monitoring of the trial	54
4.10	Assessment of PrEP use.....	58
4.11	Randomization.....	58
4.12	Blinding	58
4.13	Statistical analyses	59
5	Selection and withdrawal of participants	72
5.1	Inclusion criteria	72
5.2	Exclusion criteria	74
5.3	Participant departure from infusion schedule or withdrawal	75
6	Study product preparation and administration	78
6.1	Study product regimen.....	78
6.2	Study product formulation	78
6.3	Preparation of study products	79
6.4	Administration	81
6.5	Acquisition of study products.....	82
6.6	Pharmacy records.....	82
6.7	Final disposition of study products.....	82
7	Clinical procedures	83
7.1	Informed consent	83

7.2	Pre-enrollment procedures.....	85
7.3	Enrollment and infusion visits	86
7.4	Post-infusion visits for HIV-uninfected study participants	87
7.5	HIV counseling and testing	88
7.6	Follow-up visits for HIV-infected participants.....	89
7.7	Follow-up visits for participants who discontinue infusions for reasons other than HIV infection.....	90
7.8	Contraception status.....	90
7.9	Urine testing	91
7.10	Assessments of reactogenicity	91
7.11	Visit windows and missed visits.....	92
7.12	Early termination visit	92
7.13	Pregnancy	93
8	HIV infection assessment and clinical response	94
8.1	HIV symptom assessment.....	94
8.2	HIV screening test (prior to randomization).....	94
8.3	HIV testing postinfusion.....	94
8.4	Endpoint adjudication.....	95
8.5	HIV infection during the study	95
8.6	Medical care for participants who become HIV infected	96
9	Laboratory.....	97
9.1	CRS laboratory procedures.....	97
9.2	Total blood volume.....	97
9.3	Assay timepoints.....	97
9.4	VRC01 mAb levels.....	97
9.5	Endpoint assays: humoral	98
9.6	ARV detection	98
9.7	Host (human) genotyping	98
9.8	Lab assay algorithm.....	99
9.9	Possible additional studies.....	99
9.10	Other use of stored specimens	99
9.11	Biohazard containment	99
10	Safety monitoring and safety review	101
10.1	Safety monitoring and oversight.....	101
10.2	Safety reporting	102
10.3	Safety pause and prompt PSRT AE review	105
10.4	Review of cumulative safety data.....	106
10.5	Study termination.....	106
10.6	Social impact reporting.....	107
11	Protocol conduct	108
11.1	Emergency communication with study participants.....	109
12	Ethical considerations	110
13	IRB/EC/RE review considerations.....	112
13.1	Minimized risks to participants	112
13.2	Reasonable risk/benefit balance	113
13.3	Equitable subject selection	113
13.4	Appropriate informed consent	113
13.5	Adequate safety monitoring.....	113
13.6	Protect privacy/confidentiality.....	114

14	Version history.....	115
15	Document references (other than literature citations).....	118
16	Acronyms and abbreviations.....	120
17	Literature cited.....	123
	Appendix A Sample informed consent form.....	137
	Appendix B Approved birth control methods for transgender men (for sample informed consent form)	156
	Appendix C Sample consent form for use of samples and information in other studies.....	157
	Appendix D Tables of procedures (for sample informed consent form).....	161
	Appendix E Sample consent form for participants with HIV infection at enrollment or during the study	163
	Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants	167
	Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants	168
	Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected.....	169
	Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection	170
	Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants	171
	Appendix K Schedule 2—Procedures at CRS for HIV-1–infected participants	172
	Appendix L Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected	173
	Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection	174
	Appendix N Protocol Signature Page.....	175

1 Overview

Title

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Primary objectives

- To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in MSM+TG
- To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in MSM+TG

MSM = men who have sex with men. TG = male-to-female and female-to-male transgender persons.

Study products and routes of administration

- VRC01: human monoclonal antibody (mAb) VRC-HIVMAB060-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered at a final volume of 150 mL intravenously (IV)
- Control for VRC01: Sodium Chloride for Injection 0.9%, USP administered at a volume of 150 mL IV

Table 1-1 Schema

			Infusion schedule (Weeks)											
			[A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80*	W104†
Group 1	VRC01 10 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	900	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	900	C	C	C	C	C	C	C	C	C	C		
Total: 2700 (900 VRC01 30 mg/kg; 900 VRC01 10 mg/kg; 900 control)														

* Due to the randomization scheme, the numbers of VRC01 and control recipients may differ slightly.

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.

† Week 104 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

Interim safety assessments will be performed for participants who reach the Week 16 visit by November 19, 2016 and also through the Week 24 visit for the first 450 enrolled participants. Infusions and enrollment will continue while these interim safety assessments are conducted. The interim safety reports will be submitted to the DSMB and to the US FDA.

Participants

2700 HIV-1–uninfected MSM and TG who have sex with men or TG, aged 18 to 50 years, in North America, South America, and Switzerland

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

24 months of scheduled clinic visits

Estimated total study duration

62 months (includes enrollment and follow-up, including follow-up for HIV-infected participants)

Investigational New Drug (IND) sponsor

DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Study product providers

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (FHCRC) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC), FHI360 (Durham, North Carolina, USA)

Statistical and data management center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), FHCRC (Seattle, Washington, USA)

DF/Net Research (Seattle, Washington, USA)

Endpoint assay laboratories

- University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)
- Duke University Medical Center (Durham, North Carolina, USA)
- FHCRC/University of Washington (Seattle, Washington, USA)
- South Africa Immunology Laboratory, National Institute for Communicable Diseases (SAIL-NICD) (Johannesburg, South Africa)

- NIAID Vaccine Immune T-Cell Antibody Laboratory (NVITAL) (Gaithersburg, Maryland, USA)
- (NIAID) Vaccine Research Center (VRC) (Bethesda, Maryland, USA)
- HPTN Laboratory Center, Johns Hopkins University (JHU) (Baltimore, Maryland, USA)
- University of Colorado, Denver (Aurora, Colorado, USA)
- Peru CTU Laboratory (Lima, Peru)
- CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil)

Study sites

Clinical Research Sites (CRSs) to be specified in the Site Announcement Memo

Safety monitoring

HVTN 704/HPTN 085 Protocol Safety Review Team (PSRT); NIAID Data and Safety Monitoring Board (DSMB)

1.1 Protocol Team

Protocol leadership

<i>Chair</i>	Lawrence Corey HVTN; FHCRC 206-667-6770 lcorey@fhcrc.org	<i>Statisticians</i>	Allan DeCamp SCHARP, FHCRC 206-667-7892 adecamp@scharp.org
<i>Chair</i>	Myron Cohen HPTN; University of North Carolina 919-966-2536 mscohen@med.unc.edu		Peter Gilbert SCHARP, FHCRC 206-667-7299 pgilbert@scharp.org
<i>Cochairs</i>	Srilatha Edupuganti Emory University 404-712-1434 sedupug@emory.edu		Michal Juraska SCHARP, FHCRC 206-667-5568 mjuraska@scharp.org
	Nyaradzo Mgodini UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe 263-4-704890 nmmgodi@uz- ucsf.co.zw		Deborah Donnell SCHARP, FHCRC 206-667-5661 deborah@scharp.org
<i>Protocol Team leader</i>	Shelly Karuna HVTN Core, FHCRC 206-667-4355 skaruna@hvtn.org	<i>Medical officers</i>	Margarita Gomez Lorenzo Vaccine Research Program (VRP), DAIDS, NIAID 240-627-3510 gomezmm@niaid.nih.gov
<i>HVTN Laboratory lead</i>	John Hural HVTN Laboratory Program 206-667-1683 jhural@hvtn.org		David Burns Prevention Sciences Program (PSP), DAIDS, NIAID 301-435-8896 burnsda@niaid.nih.gov

Other contributors to the original protocol

<i>HVTN Core medical monitor</i>	Shelly Karuna HVTN Core, FHCRC	<i>DAIDS Protocol pharmacist</i>	Katherine Shin DAIDS, NIAID 240-627-3047
<i>Bioethics consultant</i>	Mark Barnes HPTN Ethics Working Group	<i>HVTN Regional medical liaison, Southern Africa</i>	Simba Takuva HVTN Core, FHCRC
<i>HVTN/HPTN Consultative investigators</i>	Ken Mayer Fenway Health, Boston, USA		

	LaRon Nelson Univ. of Rochester Rochester, NY, USA	<i>HVTN Regional medical liaison, South America</i>	Robert De La Grecca HVTN Core, FHCRC
	Manuel Villarán IMPACTA, Lima, Peru	<i>HVTN Clinical safety specialist</i>	Maija Anderson HVTN Core, FHCRC
	Sinead Delany-Moretlwe Wits Reproductive Health and HIV Institute, Johannesburg, South Africa	<i>HVTN Statistical research associates</i>	Nidhi Kochar SCHARP, FHCRC
<i>Product developer representatives</i>	John Mascola VRC		Abby Isaacs SCHARP, FHCRC
	Barney Graham VRC		Jing Wang SCHARP, FHCRC
	Julie Ledgerwood VRC	<i>HVTN Social behavioral scientist</i>	Michele Andrasik HVTN Core, FHCRC
<i>HVTN Laboratory Program representatives</i>	On Ho HVTN Laboratory Program, FHCRC	<i>HPTN LOC director</i>	Nirupama Sista HPTN LOC, FHI360
	David Montefiori HVTN Laboratory Program, Duke Univ., Durham, NC, USA	<i>HPTN Clinical research managers</i>	Philip Andrew HPTN LOC, FHI360
	Robert Coombs University of Washington Virology Specialty Laboratory, Seattle, WA, USA		Elizabeth Greene HPTN LOC, FHI360
<i>HPTN Laboratory Center representatives</i>	Susan Eshleman HPTN Laboratory Center (LC), Johns Hopkins Univ., Baltimore, MD, USA	<i>HVTN Clinical trials manager</i>	Carissa Karg HVTN Core, FHCRC
	Vanessa Cummings HPTN LC, Johns Hopkins Univ.	<i>HPTN SDMC Associate director</i>	Lynda Emel SCHARP, FHCRC
	Estelle Piwowar-Manning HPTN LC, Johns Hopkins Univ.	<i>HVTN SDMC Program manager</i>	Gina Escamilla SCHARP, FHCRC
<i>HVTN Regulatory affairs</i>	Megan Brandon HVTN Core, FHCRC	<i>HVTN Protocol development manager</i>	Carter Bentley HVTN Core, FHCRC
<i>Clinic coordinators</i>	Debora Dunbar University of Pennsylvania, Philadelphia, PA, USA	<i>HVTN Communications unit representative</i>	Jim Maynard HVTN Core, FHCRC
	Ana Patricia Rimachi Quiroz Asociación Civil Selva Amazónica, Iquitos, Peru	<i>HVTN Community engagement unit representative</i>	Gail Broder HVTN Core, FHCRC
	Christie Heiberg Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa	<i>HPTN Community program associates</i>	Jonathan Lucas HPTN LOC, FHI360

<i>Community Advisory Board (CAB) members</i>	Mark Hubbard Vanderbilt University Nashville, TN, USA		Jontraye Davis HPTN LOC, FHI360
	Likhapha Faku HVTN Global CAB Member at Large Rustenberg, South Africa	<i>Community educator/recruiters</i>	DaShawn Usher New York Blood Center, New York, NY, USA
	Jim Wick Bridge HIV CAB, San Francisco, CA, USA		Luciana Kamel Instituto de Pesquisa Clinica Evandro Chagas (IPEC), Rio de Janeiro, Brazil
		<i>HVTN Technical editor</i>	Erik Schwab HVTN Core, FHCRC

2 Background

2.1 Rationale for trial concept

Effective biomedical interventions are needed to reduce the acquisition of HIV. The global HIV-1 epidemic continues and while many countries have made progress toward leveling HIV prevalence over the last few years, micro-epidemics of infection continue to occur in nearly all regions, even in countries possessing the full toolkit of proven prevention approaches [1-4]. The World Health Organization (WHO) estimates that there were 2 million new HIV infections worldwide in 2014, the last year for which data are available [5].

Antiretroviral drugs (ARVs) have been shown to be effective for HIV prevention in serodiscordant couples when administered to HIV-infected individuals as treatment as prevention (TasP) and clinical trials are now underway to evaluate the efficacy of TasP at a population level [6]. ARVs have also been shown to be effective as pre- or post-exposure prophylaxis (PrEP or PEP) [7]. At present daily oral emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Truvada) is the only drug approved for PrEP use, but this drug combination has significant known side effects [8]. The requirement for daily use and the side effect profile have made adherence to this drug regimen challenging, especially over long periods of time [9]. As a consequence, the capacity of currently available ARV regimens to reduce HIV incidence or prevalence is less than optimal. Furthermore, sustained use of ARVs for HIV prevention will increase the already significant burden of ARV manufacturing and delivery for HIV treatment, especially in countries bearing the highest burden of HIV disease. For these reasons, a biomedical HIV prevention approach that exhibits sustained activity over an extended time period, that has a safety profile acceptable for healthy persons, and whose effectiveness is less dependent upon individual adherence, is still needed.

An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies, a strategy that has been employed for more than 100 years against diverse disease targets and that is still used for hepatitis A and B prophylaxis [10,11] and for PEP for rabies, measles, varicella zoster, and other infectious diseases [12]. Most notably, palivizumab has been used for respiratory syncytial virus (RSV) prophylaxis in pre-term and other high-risk infants for nearly two decades. In 1998, a multinational, randomized controlled trial showed that palivizumab administered during the RSV season reduced RSV-associated hospitalizations by 39–78% in premature infants and in children with bronchopulmonary dysplasia [13]. Subsequent studies have confirmed palivizumab's safety, efficacy, and clinical benefit for infants at high risk for RSV infection [14,15]. Hence, palivizumab serves as a model for the use of mAbs to block a mucosally-acquired infection. Significantly, passive administration of this antibody has also set a standard by which candidate RSV vaccines are evaluated, by defining antibody levels that effectively inhibit fusion by RSV. This precedent has informed the conceptual framework for this study.

Over the past several years, there has been a concerted and notably successful effort to isolate broadly neutralizing antibodies (bnAb) to HIV-1 from chronically infected donors [16-32]. Subsequent research has provided considerable insight into the sites these antibodies target on HIV-1 and their functionality (ie, the mechanisms by which they

neutralize the virus) [19,20,29,33]. This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies [34-37], prompting optimism that vaccines that elicit bnAbs against HIV-1 can be developed [35,38]. In addition, the availability of bnAbs against HIV opens the exciting possibility of antibody-mediated prevention (AMP) of HIV infection.

The Vaccine Research Center (VRC), NIAID, NIH has developed VRC01, a broadly neutralizing human mAb that targets the HIV-1 CD4 binding site [18]. This mAb was originally discovered in a participant infected with HIV-1 for more than 15 years who maintained viral control without use of antiretroviral therapy (ART) [39]. VRC01 has the capacity to neutralize a broad range of HIV-1 strains in vitro (Section 2.3) and has conferred protection against simian-human immunodeficiency virus (SHIV) challenges in nonhuman primate (NHP) studies [40-49] (Section 2.8). It has an acceptable safety profile, as seen in previous phase 1 studies (Section 2.9).

In addition to potentially developing a new HIV prevention modality, evaluating the preventive efficacy of mAbs can be expected to inform future HIV vaccine development. An important requisite for designing vaccines that elicit bnAbs is determining the level of neutralizing activity required to achieve a reasonable degree of protection in humans. It will also be important to know whether such levels vary by route of infection or neutralizing sensitivity of the infecting isolate. Notably, VRC01 contains the Fc portion of IgG1 and has demonstrated other effector functions. Evaluating the role of antibody-mediated effector functions (eg, antibody-dependent cellular cytotoxicity [ADCC], antibody-dependent cellular phagocytosis [ADCP], antibody-dependent cell-mediated viral inhibition [ADCVI], antibody-mediated virion capture in mucus, or inhibition of viral translocation across epithelial barriers, etc.) in protection is also of critical importance (see, eg, [50-53]).

Although it is not anticipated that this trial will lead directly to licensure, further assessment of this VRC01 product will depend on the results of this and other studies.

2.2 bnAbs to HIV-1

The last several years have seen a marked increase in the number of well-characterized bnAbs to HIV-1. Figure 2-1 shows the names and binding sites of many of these.

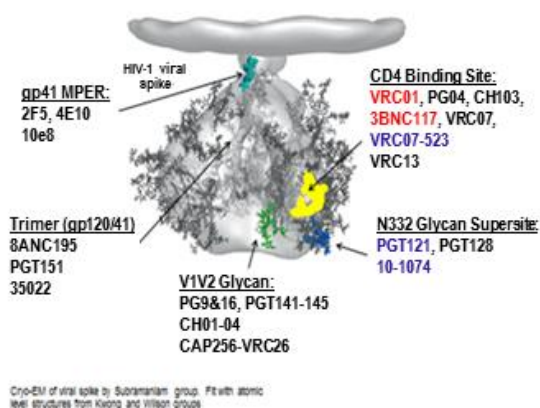


Figure 2-1 Neutralizing antibody epitopes on native Env trimer

As shown in Figure 2-2, several of these antibodies have shown considerable breadth of neutralization in in vitro testing.

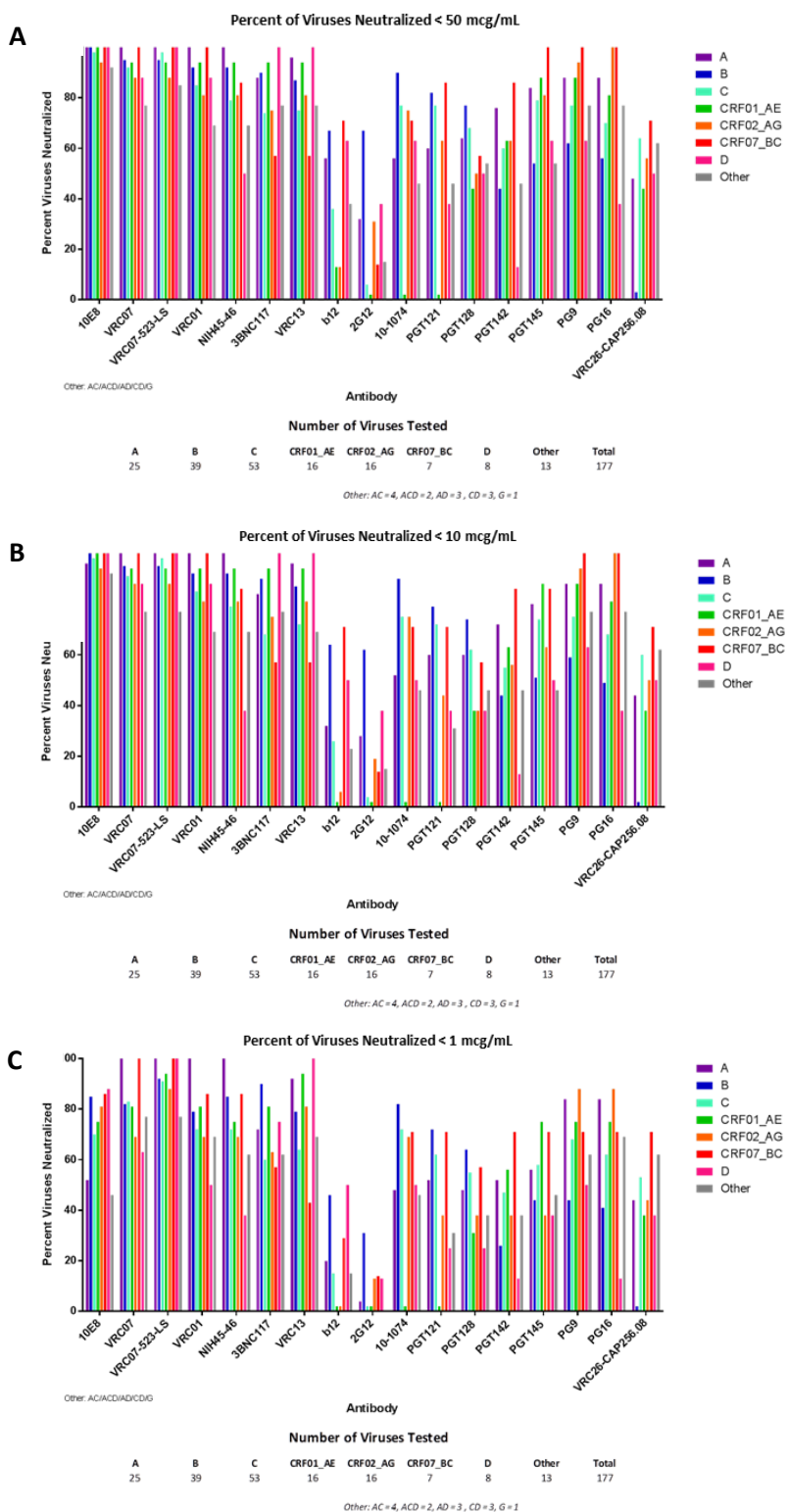


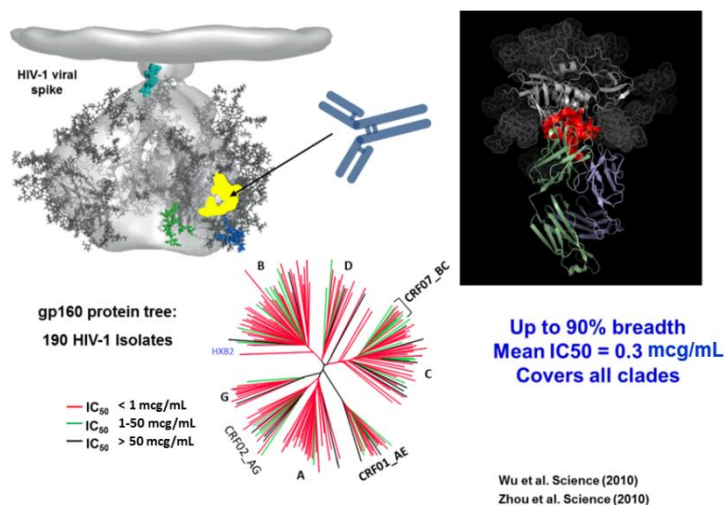
Figure 2-2 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL [32,49,54-57].

Two antibodies to the CD4 binding site of the HIV-1 envelope, VRC01 and 3BNC117 (highlighted in red in Figure 2-1), have entered phase 1 clinical trials.

2.3 VRC01: VRC-HIVMAB060-00-AB

VRC01 is a human mAb, developed by VRC/NIAID/NIH, directed against the CD4-binding site of HIV-1. The bulk lot of the drug substance was manufactured under current Good Manufacturing Practice (cGMP) conditions in a Chinese Hamster Ovary (CHO) cell line and the drug product vials were filled and labeled at the VRC Vaccine Pilot Plant (Frederick, Maryland, USA) operated by Leidos Biomedical Research, Inc. (formerly SAIC-Frederick), Frederick, Maryland (USA). Product is vialled at a concentration of 100 mg/mL VRC01 in formulation buffer containing 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. VRC01 was produced using recombinant DNA technology. Briefly, using polymerase chain reaction (PCR) amplification and cloning of the heavy and light chain variable region genes, a mAb was initially isolated from a single B cell from an HIV-1–infected subject who displayed bnAbs. VRC01 is an IgG1 antibody and is highly somatically mutated from the germ-line precursor.

The VRC01 antibody has been well characterized preclinically and has demonstrated favorable characteristics in potency and half-life [19]. In addition, it has demonstrated protection in NHP challenge studies (see Section 2.8.1 below). Figure 2-2 shows graphically the impressive breadth of VRC01, with 90% of 190 HIV-1 isolates across all clades tested showing sensitivity to neutralization by VRC01. As shown in Figure 2-3, VRC01 has a 50% inhibitory concentration (IC_{50}) of < 50 mcg/mL against 91% of primary HIV-1 isolates and IC_{50} < 1 mcg/mL against 72% of HIV-1 isolates. Notably, the IC_{50} for the vast majority of HIV-1 isolates tested is < 1 mcg/mL; the geometric mean IC_{50} for HIV-1 strains from all clades tested is 0.33 mcg/mL.



Virus clade	Number of viruses	IC ₅₀ < 50 mcg/mL	IC ₅₀ < 10 mcg/mL	IC ₅₀ < 1 mcg/mL
A	22	100%	100%	95%
B	49	96%	94%	80%
C	38	87%	84%	66%
D	8	88%	88%	50%
CRF01_AE	18	89%	83%	61%
CRF02_AG	16	81%	75%	56%
G	10	90%	90%	90%
CRF07_BC	11	100%	91%	45%
Other	18	83%	83%	78%
Total	190	91%	88%	72%

Figure 2-3 CD4 binding site antibody: VRC01 [18,19]

Details on VRC01 composition and manufacturing can be found in the investigator's brochure (IB).

2.4 Trial design rationale

Several considerations inform the design of this test-of-concept phase 2b study. The first is to establish that passive administration of bnAbs can block HIV acquisition. Based on data from in vitro neutralization studies, the NHP challenge studies described below, and pharmacokinetic (PK) data from the phase 1 clinical trials VRC 602 and HVTN 104, the doses selected are designed to elucidate the activity of the antibody across a range of serum concentrations in a diverse population of at-risk persons in multiple geographic regions of the world. The study is designed to define the optimal dosage for widespread use of the antibody or its subsequent derivatives as well as to benchmark the types of effector functions associated with efficacy, thus constituting an important bridge to other types of bnAbs and other bnAb delivery systems.

Inclusion of different doses (ie, in a 3-arm study) is important for a number of reasons. First, while the in vitro and NHP challenge data are informative, the VRC01 antibody serum level required to provide protection against HIV-1 infection in humans is unknown. Some studies suggest that transmitted-founder HIV strains may be more sensitive to neutralization than other strains (particularly by VRC01) [58,59], and therefore potentially susceptible to even lower antibody doses than those suggested by SHIV challenge studies in NHP. It must also be recognized that the lowest challenge

doses used in the NHP model likely exceed natural exposure in the majority of transmissions in humans.

Defining the lowest efficacious VRC01 dose is essential for establishing a target product profile (TPP), including optimal dosing for clinical use, for this antibody and its derivatives. Typically, higher doses of drug products are associated with lower tolerability due to side effect profiles or operational features such as length of drug administration time (eg, IV infusion time). At present the high dose (30 mg/kg) cannot be administered subcutaneously (SC), limiting the feasibility of long-term clinical use. The extreme difficulty of scaling IV administration to the populations most in need of protection against HIV infection and the complexity and cost of manufacturing mAbs would severely limit implementation of this potentially important HIV prevention tool if higher doses are required for efficacy. Therefore, it is important to evaluate the efficacy achieved at lower antibody concentrations. That lower doses of mAbs may prevent HIV acquisition is supported by the high percentage of isolates susceptible in vitro to antibody concentrations as low as 1 mcg/mL of VRC01, 1/10 the mean trough level anticipated with 30 mg/kg VRC01 dosing every 8 weeks.

Including a range of doses in this study also facilitates evaluation of antibody effector functions, in addition to neutralization, that are associated with protection (eg, virion binding, ADCC, ADCP). Note that the relationship of these important functions to neutralization is not linear and therefore cannot be inferred directly. This information will have important implications for the development of other bnAbs and other biomedical HIV prevention modalities.

Hence, in addition to providing a test of concept for AMP for HIV, if breakthrough infections are observed, the data generated by this trial will help guide development of functionally-enhanced mAbs and of long-term delivery strategies (eg, vaccine immunogen or vectored immunoprophylaxis). This trial affords a unique opportunity to correlate serum antibody levels and the potency of effector functions with protective efficacy in a trial in which these parameters can be measured close to the time of HIV acquisition, providing benchmarks for vaccine development and helping define “targets” of antibody effector mechanisms for protein or viral vector based vaccines. The data will also provide critical information by which to identify which NHP models (eg, SHIV challenge stocks) are most predictive of bnAb efficacy in humans.

2.4.1 Cohort selection

The study will be conducted among 2700 men and TG in North America, South America, and Switzerland who have anal sex with men or TG partners. The trial sample size is designed to provide 90% power to detect a prevention efficacy (PE) of 60% (rejecting the null hypothesis of 0% PE), based on reasonable assumptions regarding background HIV-1 incidence, retention, and frequency of infusions.

With respect to HIV incidence, over the past 25 years, MSM and TG who have sex with men have been the only risk groups in the US for which estimated HIV incidence has increased, with more recent increases in incidence noted particularly among young MSM of color [60,61]. In the US, Latin America, and Switzerland, MSM and TG account for more than half of new HIV infections [60,62-64]. In 2013, the estimated rate of new HIV diagnoses among Hispanic/Latino males was three times the rate of White males and 79% of these infections were attributed to male-to-male sexual intercourse [65]. Among gay and bisexual men, Black MSM – especially those between the ages of 13 and 24 –

are most affected by HIV [66]. Indeed, the HPTN 061 study found incidence of almost 6% annually among young Black MSM [67]; this is far higher than HIV incidence reported previously in White MSM. A second study found higher HIV prevalence in Black MSM than in White MSM [68].

We note that a parallel study assessing the safety and preventive efficacy of VRC01 is being conducted among 1500 women in sub-Saharan Africa who are at risk of acquiring HIV-1 through sexual contact. That study, designated HVTN 703/HPTN 081, will be conducted over approximately the same time period as HVTN 704/HPTN 085.

2.4.2 Dose and schedule

An equal number of study participants will be randomized to receive VRC01 mAb by IV infusion at a dose of 10 mg/kg or 30 mg/kg every 8 weeks or to receive the control by infusions every 8 weeks. The 8 week infusion interval represents approximately 4 half-lives of the study drug (half-life ~14 days based on previous clinical testing; see the IB).

Infusions will continue for 72 weeks for all groups, with a final primary follow-up visit (without infusion) at week 80 and an additional 24 weeks of follow-up without infusions. Hence, the study duration for each participant is 104 weeks (2 years).

Projected serum concentrations of VRC01 are shown in Figure 2-4. This figure plots predicted median VRC01 serum concentrations over time based on PK models for VRC01 administered at 10 mg/kg every 8 weeks (Panel A) and for VRC01 administered at 30 mg/kg every 8 weeks (Panel B). The plots include shaded regions illustrating time regions where the study participants have serum concentrations in low, medium, and high ranges. Based on in vitro neutralization studies (see Section 2.3) and NHP challenge studies (see Section 2.8.1) and assuming that these accurately predict protection in humans, the expected trough levels of VRC01 are projected to be an order of magnitude higher than the levels required to protect against a majority of circulating HIV-1 strains.

See Section 2.9.3 and Figure 2-9 for VRC01 serum concentrations reported to date for participants administered 10mg/kg and 30mg/kg of VRC01 every 8 weeks in HVTN 104.

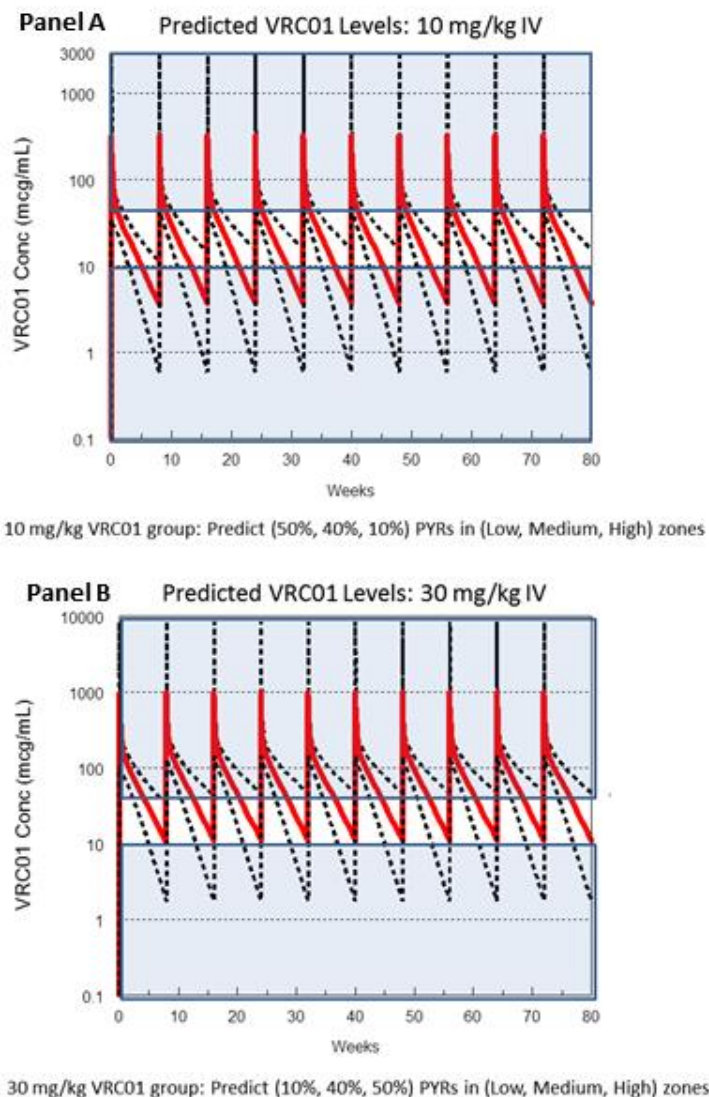


Figure 2-4 Predicted VRC01 serum concentrations over time. Panel A: Predicted VRC01 median serum concentration over time (solid lines) for 10 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72, with 95% confidence intervals (CI) (dashed lines). The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. Panel B: Predicted median VRC01 serum concentration over time for 30 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72. The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. PYR = person-year at risk.

There is a substantial overlap in the mAb concentrations between the low and high dose groups during a considerable period of time after each infusion. This is shown in Figure 2-5.

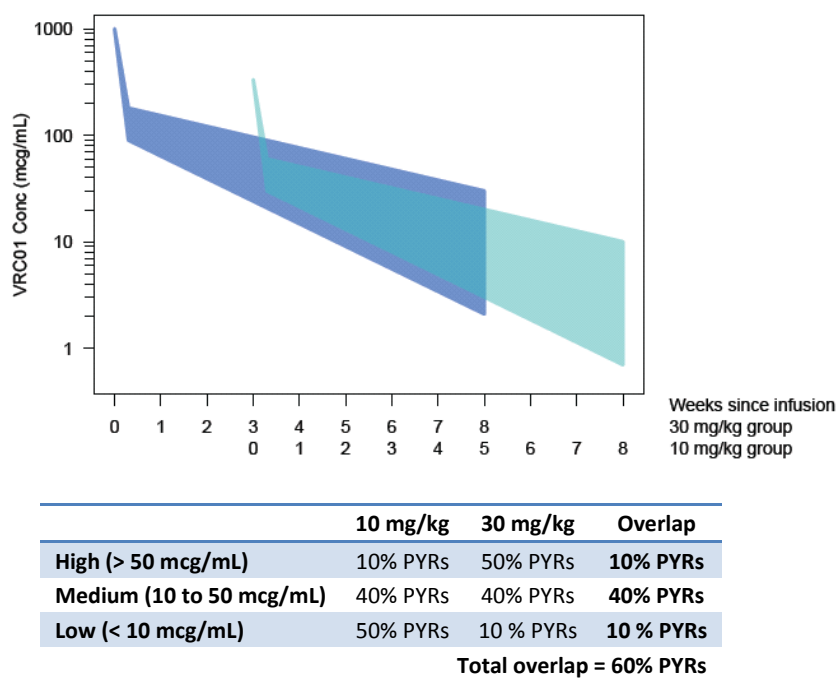


Figure 2-5 Projected overlap in serum VRC01 concentrations and PYRs of HIV exposure between high dose (30 mg/kg) and low dose (10 mg/kg) VRC01 administration

2.4.3 Choice of control

Sodium Chloride for Injection 0.9%, USP (referred to as Control) administered IV at a volume of 150 mL will serve as an inert control.

Use of a placebo control in this trial is warranted based on the scientific and public health importance of the questions it seeks to answer, the necessity of a placebo control in order to assess VRC01 efficacy in preventing HIV-1 infection, and an acceptable risk/benefit ratio considering the minimal risk associated with the placebo control selected and its administration via a procedure commonly used in clinical care. In addition, the placebo control is essential to maintain double-blinding to ensure unbiased assessments of study product safety and efficacy, and the use of the placebo control is disclosed fully to study participants (see Section 10 of Appendix A). Hence, this trial meets the standards commonly required for ethical use of placebo controls in clinical trials [69-71].

2.4.4 HIV diagnostic testing

HIV diagnostic testing will be scheduled at least every four weeks and at any time following participant report of possible exposure during the study. See Section 8 for further detail on HIV-infection assessment. Participants who are diagnosed with HIV infection after enrollment will not receive additional infusions. Infusions will also be permanently discontinued for participants who have 2 reactive HIV tests, even if subsequent testing indicated that the participant is not HIV infected.

Based on the schedule of testing, it is possible that a newly infected participant may receive an infusion of VRC01 (or Control). This does not appear to pose a safety risk for participants based on existing preclinical, clinical, and in vitro data. Specifically,

passively-infused VRC01 given to NHP on Day 7 after SHIV SF162P3 infection reduces viremia and does not cause clinical harm (see IB). Additionally, passive transfer of neutralizing antibodies (at non-protective levels) prior to infection improved control of SHIV viremia and was associated with early nAb development in infected infant macaques [72]. Furthermore, VRC01 has been evaluated in viremic and aviremic HIV-infected participants (see Section 2.9.1). VRC01 administration is associated with statistically significant transient reductions in HIV viral load in adults with chronic HIV infection (see IB), and HIV variants that escape from in vitro VRC01 neutralization have reduced viral fitness [73]. Studies evaluating VRC01 in acutely infected subjects are being initiated based on these data.

2.4.5 Trial monitoring

As this is the first large-scale phase 2b study with IV administration of a biomedical intervention for prevention of sexual HIV-1 transmission, the trial design includes an early feasibility check. After approximately 120 participants have completed the Week 32 visit, a treatment-blinded analysis of infusion feasibility will be conducted and reported to the DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq 80\%$ of those 120 participants remain engaged in the trial and have not declined further infusions. Enrollment will not be paused for this feasibility assessment.

In addition to the feasibility assessment, the study design includes sequential monitoring for potential harm, non-efficacy, high efficacy, and futility for assessing prevention efficacy. Following similar monitoring procedures developed and implemented for the HVTN 505 phase 2b vaccine efficacy trial, potential harm monitoring is maximally vigilant by testing for a higher HIV infection rate in the pooled mAb group versus the control group after each HIV infection and providing the results to the DSMB after each infection starting with the 20th total infection pooled over the study groups. This ensures that any potential risk of increased HIV acquisition (negative prevention efficacy [PE]) would be detected as early as possible, such that infusions of the mAb could be discontinued expeditiously. In addition, the operating characteristics of the trial (Figure 4-3 and Table 4-2) show that this potential harm-monitoring approach has a low risk of stopping the study prematurely if the true PE is 0% or higher. The non-efficacy monitoring is conducted approximately every 6 months, and is based on a trigger specified in the study monitoring plan.

At the 6-month intervals, statistical interim analysis reports are provided to the DSMB. Gilbert et al [74] describe the conceptual approach to the sequential monitoring of PE, where the implementation for the current trial is slightly different. Additional information is provided in Section 4.9. Full details regarding implementation of monitoring for this trial are contained in a separate trial monitoring plan.

2.5 Combination Prevention for HIV acquisition

Participants in all arms of the study will be provided with a comprehensive HIV prevention package consistent with all HIV prevention clinical trials. This package includes evidence-based behavioral risk reduction counseling [75], free condoms and lubricant, explanation and referral for post exposure prophylaxis (PEP) when indicated, and access to oral pre-exposure prophylaxis (PrEP, see below). These activities can be expected to reduce HIV acquisition below historical levels for MSM. The contribution of these efforts will be monitored. Further details on these efforts are provided in the HVTN

704/HPTN 085 Study Specific Procedures (SSP) and the HVTN 704/HPTN 085 website. It should be emphasized that because the benefit of VRCO1 monoclonal antibody is unknown, subjects in each arm of the study will receive the same prevention package.

2.5.1 Evidence for PrEP efficacy

Multiple studies in multiple settings have established that daily or pericoital FTC/TDF can be highly efficacious in preventing HIV infection in MSM [7,76-80] (see Figure 2-6). In addition, evidence suggests that less than perfect adherence to a daily FTC/TDF regimen may still provide protection against infection in MSM. For example, post hoc analyses from the open label extension to the iPrEx study (iPrEx OLE) suggest that consuming 4 tablets of TDF-FTC per week is required to confer protection [76].

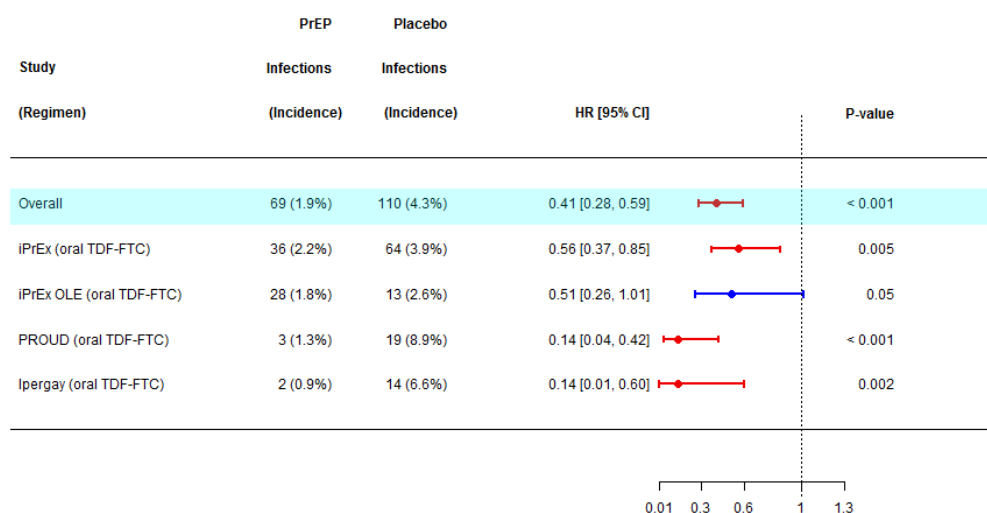


Figure 2-6 Clinical trial efficacy summary of FTC/TDF in MSM

2.5.2 Evolving PrEP guidelines

Guidelines for use of fixed dose FTC/TDF for HIV prophylaxis have evolved rapidly. In 2011, the US Centers for Disease Control and Prevention (CDC) issued interim guidelines for use of FTC/TDF as PrEP for high-risk MSM [81]. In 2012, the US FDA approved FTC/TDF for HIV prophylaxis in persons at high risk for HIV infection. That same year, the World Health Organization (WHO) issued guidance on the use of PrEP for serodiscordant couples and for men and TG women who have sex with men [82]. In 2014, the US CDC issued a further PrEP guidance document and a Clinical Provider Supplement confirming the previous recommendation of FTC/TDF PrEP as a prevention option for sexually-active adult MSM at substantial risk of HIV acquisition and expanding the recommendation to include adult heterosexually active persons at substantial risk of HIV acquisition [83,84]. PrEP has since been incorporated into WHO guidelines for ARV use for HIV treatment and prevention [85,86]; a revised and more comprehensive WHO PrEP guideline is anticipated in 2016.

2.5.3 Operationalizing PrEP access

While PrEP *efficacy* has been demonstrated and is reflected in international guidelines, PrEP's *effectiveness* depends strongly on uptake and adherence. Only 62% of iPrEx and other PrEP trial participants who were eligible to enroll in iPrEx OLE chose to do so;

those who declined cited concerns about taking a daily pill and about side effects, among other reasons. Further, among those who chose to enroll, only 76% actually initiated PrEP [76]. Hence, only about 47% of those eligible initiated PrEP in iPrEx OLE. PrEP uptake would seem even less certain among individuals who have not previously chosen to participate in an FTC/TDF PrEP trial.

Limited PrEP uptake has been seen in other settings as well. In a recent PrEP demonstration project in San Francisco, Washington DC, and Miami, 60% of those eligible chose to initiate PrEP [87]; in the demonstration project PrEP Brasil, 51% of MSM elected to start PrEP [88]. Results from HPTN 073, a trial designed specifically to address open label, volitional FTC/TDF uptake and usage in 226 African American MSM in the US, are anticipated in early 2016.

Beyond experience in clinical trials and demonstration projects, questions remain about retention and adherence to PrEP in the longer term. Notably, trials of PrEP to date have been conducted among individuals specifically self-selecting for PrEP, and generally over limited time horizons.

The continued need for additional HIV prevention tools does not negate the importance of PrEP as a critical part of the HIV prevention toolkit. Accordingly, access to FTC/TDF PrEP at no drug cost will be offered as part of a complete HIV prevention package to every HVTN 704/HPTN 085 participant through a model initially developed with extensive, multi-stakeholder input for the HVTN 505 trial [89,90]. In this model, Gilead provided fixed dose FTC/TDF (ie, Truvada) at no cost to interested HVTN 505 participants, who obtained it through prescribers independent of the trial, thus facilitating the establishment of a provider-patient relationship that could endure beyond the duration of the trial. Availability of free FTC/TDF was indicated in the informed consent document and communicated to study participants in follow up visits. However, fewer than 15% of participants in the HVTN 505 trial have reported using PrEP at any time during the trial (in which follow-up remains ongoing).

The past few years have seen increasing educational efforts and community awareness of the importance of PrEP in preventing HIV infection among MSM and we expect to see increased uptake of this prevention modality over the course of this trial. For self-selected participants under active medical care, PrEP can be very effective [91].

Consistent with this approach, Gilead Sciences has agreed to provide Truvada as PrEP for trial participants at no drug cost to them for the duration of their trial participation. This will be accomplished through the HVTN 704/HPTN 085 PrEP Referral Program in North America for US participants. This program integrates PrEP into the care provided by participants' primary health care provider, ensuring that appropriate screening assays are performed and that drug interactions are monitored over time. Outside the US, participants will participate in PrEP demonstration projects in Peru and Brazil, countries in which Truvada is not yet licensed for HIV prophylaxis but where such demonstration projects are being encouraged. In Switzerland, the CRS will directly provide Truvada at no drug cost to interested participants. In this way, PrEP access will be provided to all participants in the trial and counseling about its availability will be provided as part of HIV risk reduction counseling, which is conducted at all infusion visits throughout the course of the study. This approach has been reviewed and approved by multiple stakeholders, including community members, medical ethicists, multiple IRBs, and the HVTN 704/HPTN 085 DSMB.

As discussed in Sections 4.10 and 9.6, periodic population-based evaluation of PrEP usage will be conducted during the course of the trial. The sample size and power calculations (see Section 4.6) and plans for trial monitoring by the DSMB (see Section 4.9 and, specifically, Section 4.9.3) have been designed to accommodate substantial PrEP uptake. If the background HIV incidence rate is too low to support evaluation of VRC01 prevention efficacy due to high PrEP uptake and adherence, these data will be made available to the DSMB, which will make recommendations to the team accordingly.

2.6 Plans for future product development and testing

VRC01 is considered to have potential value for both preventive and therapeutic purposes across broad geographic regions of the HIV-1 epidemic. The product was initially evaluated in phase 1 studies to characterize PK and distribution in HIV-infected and HIV-uninfected adults (VRC 601 and 602, respectively; see Sections 2.9.1 and 2.9.2) and PK and safety for multiple administrations under several route and dosing regimens are being evaluated currently (HVTN 104; see Section 2.9.3). In parallel, IMPAACT P1112 will evaluate the safety of VRC01 in high-risk infants born to HIV-infected mothers; data from this study will support a future evaluation of the efficacy of VRC01 administered to high-risk infants shortly after birth and continued through the period of breast-feeding for prevention of mother-to-child HIV transmission (PMTCT).

The development of VRC01 for clinical use depends on a number of factors, the most critical of which is the level of efficacy demonstrated by the current study. If the antibody proves to be highly effective at preventing HIV-1 infection, its development will depend on identifying a partner able to provide large-scale manufacturing. Other factors that could influence advanced development of VRC01 or similar monoclonal antibodies include: 1) the potential for improving the potency of the product to allow use at a lower dose and perhaps by an SC route, 2) the potential for increasing the half-life of the product to allow less frequent dosing, and 3) the potential to use VRC01 or its derivatives in combination with other neutralizing mAbs to increase potency and breadth of coverage. Efforts to address these issues are proceeding in parallel with the current study, but the outcome of the current study will have the greatest influence on the future clinical use of VRC01 in adult prevention or PMTCT.

2.7 Preclinical safety studies

2.7.1 Preclinical toxicology and PK study of VRC01 in rats

Table 2-1 Summary of preclinical studies

Study number	Product	Type of study	Animal	N	Dose groups	Route	Schedule
SRI No M896-11	VRC-HIVMAB060-00-AB	Repeat dose toxicity	Sprague-Dawley rats	10m, 10f each 50m, 50f total	Vehicle* 4mg/kg IV 40 mg/kg IV 400 mg/kg IV 40 mg/kg SC	IV & SC	D1, D8
SRI No M896-11	VRC-HIVMAB060-00-AB	Single-dose PK	Sprague-Dawley rats	9m, 9f each 27m, 27f total	4 mg/kg IV 40 mg/kg IV 40 mg/kg SC	IV & SC	D1

* Vehicle consists of VRC01 formulation buffer.

A repeat dose toxicity study of IV and SC administration and a single dose PK study was performed by SRI International (Menlo Park, CA) with VRC01 in male and female Sprague-Dawley rats in accordance with US FDA “Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies” (Table 2-1). This study was conducted with a pre-GMP pilot lot of VRC01 manufactured at smaller scale using a similar purification process to that of the GMP clinical grade drug product.

For the safety assessment, various doses of VRC01 (4 mg/kg, 40 mg/kg, or 400 mg/kg) or a comparable control vehicle was administered by tail vein infusion on Days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via SC administration to the dorsal scapular region on Days 1 and 8. Each group contained 10 male and 10 female rats. Five animals of each sex were sacrificed on Day 9, one day after the second administration; the remaining animals were sacrificed on Day 30, 22 days after the second administration.

Results obtained showed that both routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, infusion site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate aminotransferase (AST) and alkaline phosphatase (ALP) on Day 9. By Day 30, AST values had returned to normal, and ALP values were returning to normal.

Other than red discoloration of the administration site in one male in the SC group on Day 9, there were no other gross necropsy observations attributable to VRC01 administration. There were no histopathology findings that were considered related to IV administration of VRC01.

The pre-specified IV dose studied in rats was 400 mg/kg and SC was 40 mg/kg, which will greatly exceed the dose levels in the adult clinical studies. A “no observed effect level” (NOEL) was not determined in this study because transient elevations of AST and ALP were observed on Day 9 after IV administration and transient inflammation at the dose site was observed on Day 9 after SC administration. Because the elevated AST and ALP levels were transient and minor and did not correlate with histopathology findings, the no observed adverse effect level (NOAEL) for VRC01 by the IV route of administration in rats was 400 mg/kg, the highest dose used in this study.

For the PK analysis, 3 groups of rats (9 males and 9 females in each group) received VRC01 on Day 1 at 4 mg/kg IV, 40 mg/kg IV, and 40 mg/kg SC respectively. VRC01 levels in serum were determined using an enzyme-linked immunosorbent assay (ELISA) with samples collected predose from each animal and from an additional 3 males and 3 females to provide untreated control serum. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following postdose timepoints: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life was about 10 days, with clearance of approximately 20 mL/day/kg and volume of distribution that was about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. VRC01 administration by the SC route resulted in mean peak serum levels at 7 days for male or 3 days for female animals. The maximum serum concentration and area under the concentration-

time curve to the last timepoint values were lower when 40 mg/kg was administered by the SC route compared with the IV route. The bioavailability of 40 mg/kg VRC01 administered by the SC route was estimated to be 31.4% (males) and 42.3% (females). After the peak concentration of VRC01 was achieved in the SC group, the serum levels decreased much more rapidly from 7 to 14 days than they did in the IV groups, and VRC01 concentrations in the SC group were not quantifiable at timepoints after 14 days. These data indicate that clearance of VRC01 in rats was markedly enhanced when it was administered by the SC route. The development of anti-drug antibodies that contribute to an increased rate of clearance is often observed in preclinical safety studies of protein-based test articles when they are not tested in the species of origin. Although immunogenicity was not examined in this study, the presence of such antibodies might have contributed to the increased rate of clearance of VRC01 after SC administration that was observed in this study [92,93].

2.7.2 Tissue cross reactivity GLP study of VRC01 with human tissues in vitro

A tissue cross-reactivity study of VRC01 using normal adult and neonatal human tissues in vitro (Testing Facility Study No. A255-12) was performed by Charles River Laboratories (Reno, NV) in accordance with U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies” (GLP). The tissue panels used as the test system for this *in vitro* cross-reactivity study included all of the tissues on the “Suggested list of human tissues to be used for immunohistochemical or cytochemical investigations of cross reactivity of monoclonal antibodies” in Annex I of the “European Medicines Agency Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use on December 18, 2008” and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997).” In addition, the tissue cross-reactivity study used additional neonate/infant tissues suggested by the FDA to support future trials in infants.

To determine the cross-reactivity of VRC01 binding, VRC01 was applied to cryosections from a full panel of tissues from normal human adults and a limited panel of human neonatal tissues, immunohistochemically detected using a biotinylated rabbit anti-human IgG secondary antibody, and binding was visualized with a streptavidin-horseradish peroxidase complex and a diaminobenzidine chromogen substrate. VRC01 binding was evaluated at concentrations of 5 and 50 mcg/mL.

Specific VRC01 staining was not observed in any normal adult human or neonatal human tissues evaluated. Therefore, in vitro evaluation of cross-reactivity in tissue specimens did not identify potential tissue sites or organ systems to more thoroughly evaluate in subsequent preclinical studies, and it supports the future use of VRC01 in humans.

2.7.3 Other toxicity studies

Several in vitro studies were conducted to assess antibody activity against self-antigens by VRC01. Several anti-HIV neutralizing mAbs will cross-react to lipid or nuclear antigens or Hep-2 cells [94,95]. Anti-lipid binding activity is understandable when considering that the HIV-1 gp41 protein is membrane-spanning and the epitopes (MPER: Membrane-Proximal External Region) recognized by some mAbs (eg, 4E10 and 2F5) are membrane-proximal and likely extend into the membrane itself. Therefore, the ability (or lack thereof) of VRC01 to cross-react with lipids was assessed in collaboration with Dr.

Barton Haynes of Duke University. Binding of antibody to cardiolipin was assessed in a luminescent assay, expressed in relative units. VRC01 was compared to 4E10, an anti-gp41 mAb known to bind to cardiolipin and nuclear antigens, and Synagis, a licensed anti-RSV antibody used as a negative control. Synagis is included because it is the licensed mAb product most analogous to the intended clinical use of the VRC mAb [13].

Individual studies are summarized in Table 2-2. Unlike other anti-HIV neutralizing mAbs, VRC01 does not react to phospholipids or anti-nuclear antigens or Hep-2 cells. Additional details are provided in the IB.

Table 2-2 In vitro preclinical safety studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC01 does not react to phospholipids
Assessment of anti-nuclear antigen reactivity	VRC01 does not react with nuclear antigens
Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT)	VRC01 does not impact aPTT by binding phospholipids
Assessment of Binding to a Human Cell Line by Immunohistochemistry	Fluorescently labeled VRC01 does not bind Hep-2 cells

2.8 Nonhuman primate (NHP) studies of VRC01

Several non-Good Laboratory Practices (ie, non-GLP) studies of VRC01 have been completed in NHP to assess for preclinical evidence of potential efficacy for prevention of HIV infection. Table 2-3 summarizes the studies performed.

Table 2-3 Summary of NHP pharmacology and challenge studies

Study	Product	Animal	N	Dose/Route	Infusion schedule	Challenge route	Challenge stock/dose	Challenge schedule
Pharmacology	VRC01 (Pilot lot)	Rhesus macaques	4f 4f	40 mg/kg IV 40 mg/kg SC	Day 0	NA	NA	NA
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4m 4m 4m	5 mg/kg IV 20 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-SF162P3 (300 TCID ₅₀ *)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4f 4f	20 mg/kg IV Human IgG IV (control)	Day 0	Intravaginal	SHIV-SF162P3 (300 TCID ₅₀)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	6m 6m 4m 16m 14m	20 mg/kg IV 5 mg/kg IV 1.25 mg/kg IV 0.3 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-BaL (TCID ₅₀ 12,800 in TZM-bl)	Day 2 postinfusion

*TCID₅₀ = 50% tissue culture infectious dose

In the pharmacology study, plasma and mucosal (ie, rectal, vaginal, and nasal) samples were collected at frequent intervals through Day 28. A dose of 40 mg/kg IV or SC in female rhesus macaques resulted in plasma concentration of VRC01 exceeding 50 mcg/mL in 7 of 8 animals at Day 14 and greater than 10 mcg/mL in 7 of 8 animals at Day 28.

Please see the VRC01 IB for more details.

2.8.1 Protection against challenge in NHP models

Both neutralizing and non-neutralizing antibodies to HIV and SIV have been shown to protect against experimental challenge in the NHP model [40-42,96-100]. In these studies the degree of protection has varied with the neutralizing potency of the antibodies and with the dose, route, and sensitivity of the challenge stocks. Low antibody concentrations have in some instances been quite protective, especially against repeat low-dose mucosal challenges [44,45]. However, neutralization-resistant SHIVs have been developed and have been shown to be resistant to protection [101,102]. This has permitted estimation of neutralization titers for different mAbs against SHIVs representing a broad range of neutralization resistance.

VRC01 has been tested in several NHP challenge experiments (see Table 2-3). In a rectal challenge model with SHIV BaLP4, a dose of 20 mg/kg IV protected 6/6 NHP; a 5 mg/kg IV dose protected 6/6; and a 0.3 mg/kg IV dose protected 2/6 [47]. Using a more resistant SHIV-162P3 challenge, a 20 mg/kg IV dose protected all 4 male animals from rectal challenge and all 4 female animals from vaginal challenge [47]. Analyses of the combined data from the NHP challenge studies show complete protection against SHIV162P3 challenge at a VRC01 plasma concentration of 50 mcg/ml and partial protection (IC_{50} [50% inhibitory concentration]) at 20 mcg/mL. For the more sensitive BaLP4 virus the IC_{50} is only 1.5 mcg/mL. Based on preclinical studies, an antibody serum concentration of about 40 to 50 mcg/mL is projected to provide protection against the vast majority of circulating strains of HIV [103]. In the NHP studies, both the virus sensitivity and serum antibody titers appear to influence protection from mucosal challenge. A summary of serum concentrations associated with protection against diverse SHIV strains of varying resistance to neutralization is shown in Figure 2-7.

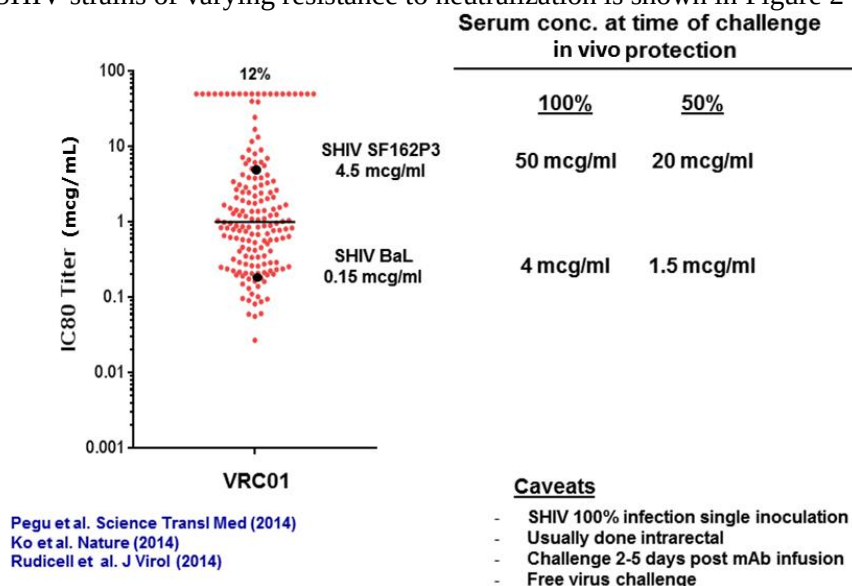


Figure 2-7 VRC01 IC_{80} values (170 Isolates) and serum concentrations in NHP SHIV challenge studies

It is particularly interesting to note that following administration of VRC01 to NHP, the antibody is found in mucosal tissues (see Figure 2-8). This is likely a product of active antibody transport to mucosal tissues through neonatal Fc receptor (FcRn) binding [48].

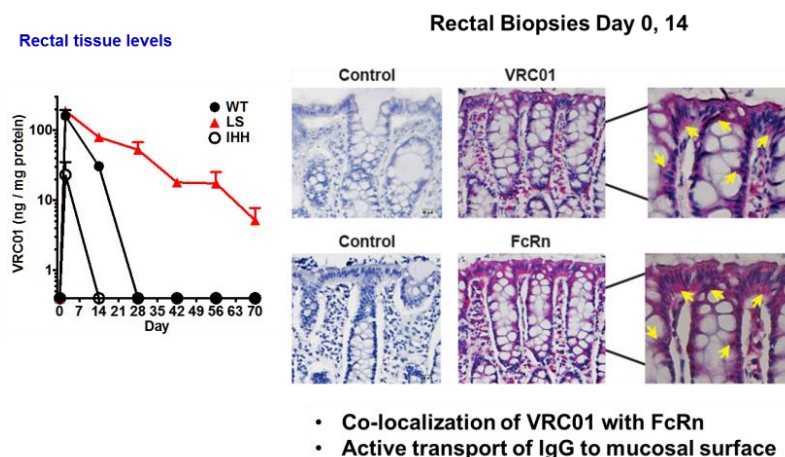


Figure 2-8 VRC01 mucosal pharmacokinetics in rhesus macaques [48]

NHP challenge studies have also shown that, in addition to classic neutralization, bnAbs such as VRC01 often elicit antibody-mediated cellular effector functions [45,104]. As a result, protection against experimental challenge has sometimes been achieved with notably low doses of VRC01 [47,103]. Similar mechanisms of protection have been implicated in studies of other bnAbs showing protection despite barely detectable neutralization activity (1:1) at challenge [44].

Recent NHP studies of VRC01 and other highly potent mAbs, such as PGT121, demonstrate protection at infusion doses of 5 mg/kg and even at 1 mg/kg [46,49,103,105]. There is also evidence that such protection can be durable; a simianized version of VRC01 was shown to protect monkeys against SHIV challenge nearly 8 weeks after their last 5 mg/kg antibody infusion, when plasma concentrations of VRC01 ranged from ~0.5 mcg/mL to undetectable [105]. These data suggest that a 10 mg/kg infusion dose of VRC01 administered every 8 weeks may offer protection against HIV acquisition.

Please see the VRC01 IB for more details on the NHP challenge studies.

2.9 Clinical trial experience

Completed phase 1 clinical studies of VRC01 include first-in-humans dose escalation studies for safety, tolerability, and PK assessments in HIV-infected (VRC 601) and HIV-uninfected (VRC 602) adults. Studies to characterize the neutralizing activity and other functional assays as a function of plasma concentration are also underway. As of April 2017, more than 1200 clinical trial participants have received VRC01 in phase 1 trials and in the phase 2b AMP studies.

Both the IV and SC routes of administration have been evaluated. Ultimately, the best route for clinical use may depend upon the age of the recipient (adult or infant), stage of product development, formulation, and important considerations related to volume needed and maintenance of a target VRC01 blood level considered to be in the therapeutic range.

2.9.1 VRC 601

VRC 601 (NCT01950325) titled, “A Phase 1, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults.”

VRC 601 (Table 2-4) was the first study of the VRC01 mAb in HIV-infected participants [106]. It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti-antibody immune responses. VRC 601 opened in September 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and in total, 23 HIV-infected participants, including 15 aviremic ARV-treated participants and 8 viremic non-ARV treated participants, were infused with one or two doses of VRC01 at doses up to 40 mg/kg IV.

Table 2-4 VRC 601 study schema

VRC 601 Dose Groups		VRC01 Administration Schedule	
Group	No. of evaluable participants*	Day 0	Week 4
1	3-5	1 mg/kg IV	1 mg/kg IV
2	3-5	5 mg/kg IV	5 mg/kg IV
3	3-5	5 mg/kg SC	5 mg/kg SC
4	3-5	20 mg/kg IV	20 mg/kg IV
5	3-5	40 mg/kg IV	40 mg/kg IV
Total	15-25	IV doses administered in 100 mL of normal saline over 30-60 minutes. SC doses administered in the minimum volume at 15 mL/hr. *Only participants who begin infusion are evaluable. Only 3 evaluable participants per group will be enrolled into the dose group until the safety review is completed. Additional slots are available, if needed, to have sufficient data for the safety review or to include at least one eligible subject with a detectable viral load later after the dose escalation is complete.	

The first infusion at 1 mg/kg IV was administered in the VRC 601 study on September 30, 2013. Beginning on March 28, 2014, the dose escalation proceeded according to the schema. The first 40 mg/kg IV administration in this study occurred May 12, 2014 and the last infusion in VRC 601 occurred on April 6, 2015. All IV and/or SC infusions have been well-tolerated with no serious adverse events (SAEs) or dose limiting toxicity.

VRC 601 demonstrated evidence of VRC01-mediated antiviral effect. An interim analysis of the VRC 601 viral load data obtained from 8 viremic adults through April 30, 2015 shows that VRC01 has a statistically significant in vivo virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking antiretroviral therapy (ART) when enrolled into the study and had not started ART during the time period when the viral load data were collected. Six of the eight adult participants had $\geq 1 \log_{10}$ copies/mL decrease in viral load and two participants had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL respectively. These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load postinfusion days 5 to 16;

- The median time to reach $\geq 0.5 \log_{10}$ decrease in viral load is 5 days; and,
- The median time to greatest decrease in viral load is 7 days.

A $0.5 \log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ART. To have clinical benefit, such a change would need to be sustained. In VRC 601, participants were administered only one dose of VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected. However, the data demonstrate a VRC01 mediated anti-viral effect.

2.9.2 VRC 602

VRC 602 (NCT01993706) is titled, “A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults.”

VRC 602 was the first study of the VRC01 mAb in HIV-uninfected adults. It was a dose-escalation study to examine safety, tolerability, dose, and PK of VRC01 [107]. VRC 602 opened in December 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and the final infusion was administered in August 2014.

As shown in Table 2-5, there were 3 open-label, dose escalation groups (Groups 1, 2, and 3) for IV administration and 1 double-blinded, placebo-controlled group (Group 4) for SC administration.

Table 2-5 VRC 602 study schema

VRC 602 Groups			VRC01 Administration Schedule	
Group	Initial Enrollments	Additional Enrollments	Day 0	Week 4
1	3	2	5 mg/kg IV	5 mg/kg IV
2	3	2	20 mg/kg IV	20 mg/kg IV
3	3	2	40 mg/kg IV	40 mg/kg IV
4	SC administration			
4A	3	2	5 mg/kg SC	5 mg/kg SC
4B	3	2	Placebo SC	Placebo SC
Total		25	20 participants treated with VRC01 at different dosage levels and 5 participants treated with placebo administered SC	
IV doses administered in 100 mL of normal saline over 1 hr. First SC dose administered at about 15 mL/hr via SC infusion pump; subject option for second dose administration (Week 4) by direct SC injection with needle and syringe.				

All IV and/or SC infusions were well-tolerated with no SAEs or dose limiting toxicity [107].

PK analysis from VRC 602 revealed a VRC01 terminal half-life of 15 days across all IV infused dose groups. After the first infusion, 28-day trough levels were 35 mcg/mL and 57 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. Following the

second infusion, the 28-day trough values rose to 57 mcg/mL and 89 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively [107].

In addition, after infusion VRC01 retained the expected neutralizing activity in serum and no anti-VRC01 antibodies were detected [107].

2.9.3 HVTN 104

HVTN 104, titled *A phase 1 clinical trial to evaluate the safety and drug levels of a human monoclonal antibody, VRC-HIVMAB060-00-AB (VRC01) administered in multiple doses intravenously and subcutaneously in different dosing schedules to healthy, HIV-uninfected adults*, is examining safety profiles and serum levels of 5 different regimens for the IV and SC administration of VRC01 (Table 2-6). IV administration is being evaluated at doses of 10, 20, 30, and 40 mg/kg; SC administration is being tested at 5 mg/kg.

Table 2-6 HVTN 104 study schema

Dose Groups		Study product administration schedule in months (days)											
Group	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	IV placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01
4	12	VRC01 10mg/kg IV				VRC01 10mg/kg IV				VRC01 10mg/kg IV			
5	12	VRC01 30mg/kg IV				VRC01 30mg/kg IV				VRC01 30mg/kg IV			
Total	88	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered by needle and syringe injection											

HVTN 104 is a phase 1 clinical trial designed to evaluate the safety and drug levels of VRC01 administered in multiple intravenous or subcutaneous doses and different dosing schedules to 88 healthy, HIV-uninfected adults at 6 HVTN CRSs in 4 US cities: Boston, New York, Philadelphia, and Cleveland. The first participant enrolled in HVTN 104 on September 9, 2014 and the last participant enrolled on July 15, 2015. Study product administration for all participants was complete as of November 30, 2015. The study has 5 arms: Group 1 is evaluating the IV administration of a 40 mg/kg loading dose, with 2 subsequent 20 mg/kg doses given at 8 week intervals. Groups 2, 4, and 5 are evaluating 3 infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg, respectively, given 8 weeks apart. Group 3 is evaluating 5 mg/kg given every 2 weeks subcutaneously for 24 weeks after an initial IV administration at 40 mg/kg; this will inform the design of perinatal prophylaxis studies. Secondary aims of HVTN 104 are: (1) to evaluate the kinetics of *in vitro* neutralization in serum of a single VRC01 sensitive virus isolate (TZM.bl assay); (2) to

determine whether anti-idiotypic antibody (AIA) can be detected and whether there is a correlation of VRC01 levels and AIA levels in serum; (3) to determine if measurable levels of VRC01 can be found in genital, rectal, and oral secretions; (4) to evaluate the kinetics of *in vitro* neutralization in mucosal secretions of a single VRC01 sensitive virus isolate; and (5) to assess binding of VRC01 to multiple Env proteins.

A total of 249 IV infusions and 208 SC injections of VRC01 were administered in HVTN 104. The infusions and injections were well tolerated, with 28% of infusions and 14% of injections associated with mild pain and/or tenderness. 55% of VRC01 and 50% of placebo recipients experienced mild pain and/or tenderness at the infusion or injection site sometime during the trial. One participant experienced moderate pain and/or tenderness following an SC injection of VRC01. Mild infusion site erythema/induration reactions were reported for 2 VRC01 participants and 1 placebo recipient. Two moderate erythema/induration reactions were reported, 1 following IV VRC01 and 1 following VRC01 SC injection. For 76% of the infusions and injections administered in the trial, no systemic reactogenicity symptoms were reported. 56% of VRC01 and 75% of placebo recipients experienced systemic reactogenicity symptoms following at least one study product administration. These were all graded as mild in the placebo recipients; of VRC01 recipients who experienced any systemic symptoms, the maximum severity was mild in 70%, moderate in 23%, and severe in 6% (3 participants). The most commonly reported symptoms were malaise/fatigue, headaches, and myalgias.

The severe systemic reactogenicity symptoms reported in 3 VRC01 recipients are detailed as follows:

- 1 participant developed severe malaise, myalgia, headache and chills, mild nausea, and moderate arthralgia symptoms within 3 days after the first infusion of study product. These symptoms had resolved by Day 7. The participant had a concomitant AE of laboratory confirmed Influenza A infection diagnosed on Day 2 and was treated with Ibuprofen.
- 1 participant reported a viral illness AE of moderate intensity beginning 3 days prior to the 9th SC injection (10th study product administration), characterized by nausea and vomiting, sore throat, runny nose but no fevers; a household contact was also ill. At baseline on Day 0 of the 9th SC injection, mild malaise/fatigue was still present. At the early assessment timepoint on Day 0, this was still present and also grade 1 nausea. Within 3 days of the injection, the participant developed severe malaise, myalgia, headache, chills, and arthralgia; these all resolved on Day 6, which was the date the AE for viral illness was resolved. There was no reported use of concomitant medications for these symptoms.
- 1 participant reported severe malaise/fatigue on the day of the first infusion, resolving spontaneously the next day. During this reactogenicity period, this participant also reported a grade 1 headache on Day, resolving the next day.

There were no study product discontinuations due to reactogenicity symptoms.

There were 235 AEs occurring in 70 participants (79.5%), with similar rates of occurrence across all treatment groups. 74% of AEs were graded as mild, 22.5% as moderate, and 3.4% as severe. 9 AEs (3.8% of all AEs) occurring in 8 participants were deemed product-related by the investigators; all were mild and transient. Those occurring

following VRC01 administration included elevations of hepatic transaminases (AST and ALT in 1 individual), elevated creatinine, neutropenia, localized injection site pruritus, diarrhea, generalized rash, and Varicella zoster infection. No VRC01-related hypersensitivity reactions or CRS symptoms were observed during the study.

Study product administration was discontinued in 8 participants. Reasons for discontinuing study product included: AEs (3 participants), relocation from study site (2), unable to adhere to visit schedule (1), unable to contact (1), and pregnancy (1). Of those participants for whom study product was discontinued due to an AE, 1 participant developed a mild, localized pruritic, maculopapular rash 3 days after receiving the first SC injection of VRC01, which resolved within 4 hours after applying inert lotion; this was deemed related to study product. Another participant had a brief syncopal episode several hours after receiving a VRC01 infusion; this was deemed not related to study product. A third participant had mild, brief chest tightness following the first SC injection that resolved spontaneously; this was deemed related to study product, however this participant was determined after unblinding to have received the placebo. In sum, VRC01 was well-tolerated when administered IV or SC.

Of note, safety experience with VRC01 has remained consistent whether 1-2 doses were administered, as in VRC 601 and 602, or multiple doses were administered, as in HVTN 104. No trends toward recurrence of lab abnormalities or AEs deemed related to study product or increase in frequency or severity of local or systemic reactogenicity symptoms has been observed with multiple administrations of VRC01.

Figure 2-9 shows serum VRC01 levels following the first 2 infusions (samples collected as of October 19, 2015) for participants in Group 4 (10 mg/kg of VRC01) and Group 5 (30 mg/kg) of HVTN 104. The number of study participants with samples assayed at each time point is shown on the X axis of each graph. As expected, trough levels following the second infusion are somewhat higher than following the first infusion. The median antibody concentration in the 10 mg/kg group is above 10 mcg/mL for approximately 37 of the 56 days (66%) following the second infusion with a median trough concentration of 4.6 mcg/mL (25-75% interquartile range 2.6 – 6.3). For the 30mg/kg group the median trough level is 9 mcg/mL (25-75% interquartile range 6.5 – 9.4).

These levels are quite similar to those modeled for the study and they show the desired overlap in concentrations achieved with the two doses selected for the study.

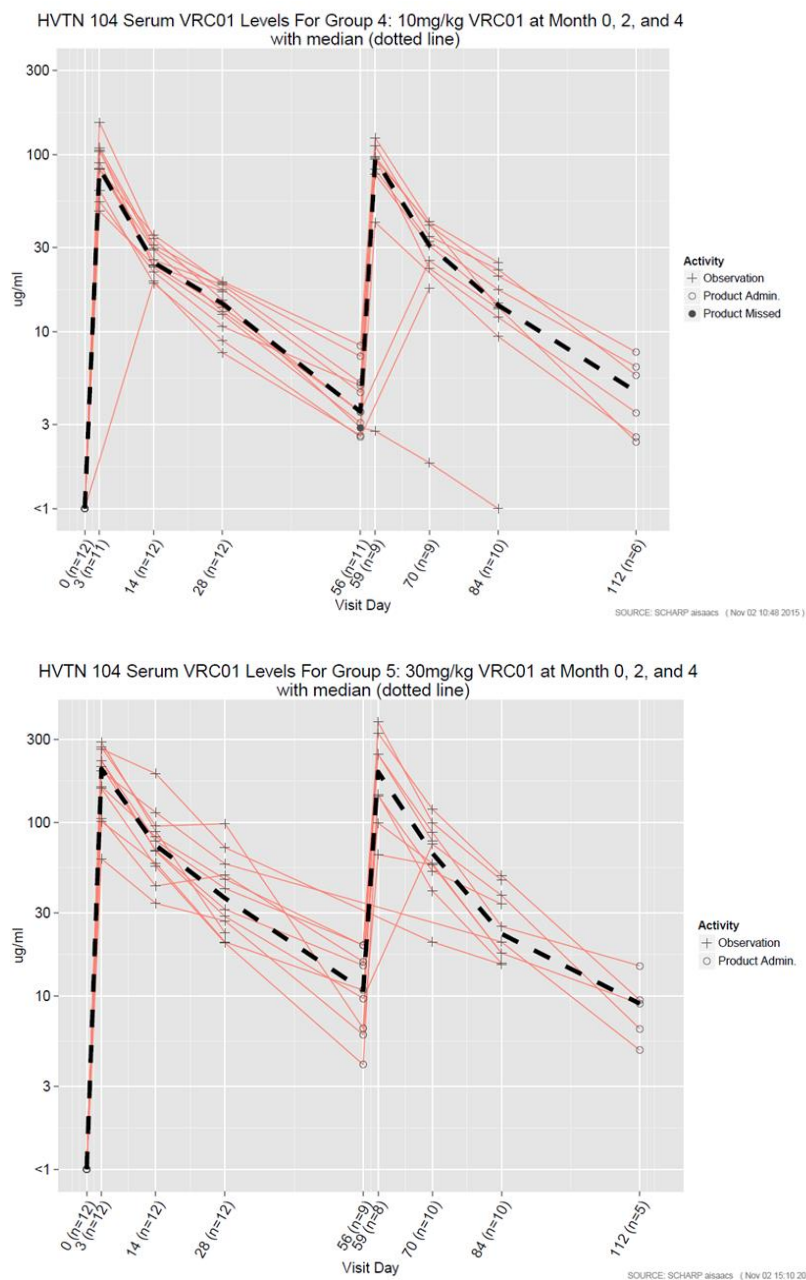


Figure 2-9 VRC01 serum levels through month 4 observed in HVTN 104 Group 4 (10mg/kg IV) and Group 5 (30mg/kg IV)

2.9.4 Safety summary of VRC01

As of February 23, 2016, approximately 130 adult participants received one or more VRC01 administrations, including 23 in VRC 601, 23 in VRC 602 (5 additional participants received placebo), and 84 in HVTN 104 (4 additional participants received placebo). 249 VRC01 infusions and 208 SC injections were given in HVTN 104.

Cumulatively, there have been no expedited safety reports to the FDA or study safety pauses for adverse events and no reactions during the VRC01 or placebo/control product administration that resulted in an incomplete administration.

VRC01 SC or IV administrations are generally associated with mild or moderate local reactions of pruritus, redness, and pain/tenderness, which resolve within a few minutes to a few hours after the administration is completed. When present, most systemic reactions after administration of VRC01 SC or IV are mild and include: malaise, myalgia, headache, chills, nausea, and joint pain.

Unsolicited AEs of grade 3 or higher severity and deemed related to study product have not been reported.

Other AEs attributed to study product administration have included mild or moderate AST elevation, alanine aminotransferase (ALT) elevation, creatinine elevation, and decreased neutrophil count. Mild or moderate elevated transaminases were reported in 4 of 21 (19%) HIV-infected participants in VRC 601 (all of whom were taking ARVs). These laboratory changes resolved spontaneously and did not require discontinuation of study product administration. Among HIV-uninfected participants in VRC 602 or HVTN 104, 1 participant had grade 1 (mild) transiently elevated ALT assessed as possibly attributed to VRC01 in the VRC 602 study and 2 participants had grade 1 (mild) transiently elevated ALT/AST values assessed as related to VRC01 in HVTN 104. These 3 participants all received VRC01.

In the HVTN 104 trial, there were 3 product discontinuations for AEs, 2 of which were deemed related to study product infusion or injection. One discontinuation was for a 20-minute episode of chest tightness occurring approximately 25 minutes after SC injection of placebo in a participant who is a chronic smoker on nicotine replacement while smoking. One discontinuation was in a participant who reported a generalized rash that began three days after SC injection of VRC01, and resolved within 4 hours with ibuprofen and the application of an over-the-counter non-steroidal cream. The third discontinuation was in a young, otherwise healthy participant who experienced a brief episode of syncope, deemed not related to study product, approximately 4 hours after IV infusion of VRC01. In addition, one person in HVTN 104 had study product discontinued due to pregnancy occurring during the trial.

Overall, VRC01 administration in the dose range from 10 to 40 mg/kg IV and at 5 mg/kg SC has been assessed as well-tolerated and safe for further evaluation.

2.9.5 Particle formation

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. In previous phase 1 studies, particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation upon thawing has no effect on product quality. For additional information, see the IB.

2.10 Potential risks of study products and administration

In a preclinical study performed in rats, there was a small dose-dependent, but transient, increase in AST and ALP, but not in ALT following IV administration. In rats, there were no histopathology findings following IV administration.

Thus far in VRC 601, VRC 602, and HVTN 104 there have been no SAEs deemed related to study product (see Section 2.9.4). Administration of mAb may have a risk of

immune reactions such as acute anaphylaxis, serum sickness, and the generation of auto-reactive antibodies; however, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs, which would have a risk of human anti-mouse antibodies [108]. In this regard, as VRC01 is targeted to a viral antigen and is a human mAb, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [108]; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

It is known from published experience with human mAbs directed against the cell surface targets on lymphocytes that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome [109]. Cytokine release syndrome and other immune reactions such as tumor lysis syndrome have been observed with administration of chimeric and humanized mAb [108]. Most infusion-related events occur within the first 24 hours after beginning administration. Specifically, with regard to cytokine release syndrome reactions, these most commonly occur within the first few hours of beginning the infusion and are more common with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, cytokine release syndrome is managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate [110]. Severe reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are infrequent and more often associated with mAbs targeted to human proteins or with a non-human mAb, such as a murine mAb [108].

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after exposure to the mAb and are noted to be more common with chimeric types of mAb [108]. Serum sickness has not been described with administration of licensed fully human mAbs.

There are several FDA-licensed mAbs for which reactions related to the rate of infusion have been described. Some symptoms may be treated by slowing or stopping the infusion.

Other side effects of licensed mAbs include infections, thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity [108].

The HVTN laboratory tested plasma from HIV-uninfected individuals that was spiked with VRC01 in a range of concentrations that encompasses those likely to be observed in this clinical trial. VRC01 did not cause a reactive test result using several standard antibody-based HIV-1/2 diagnostic tests used in the US. However, VRC01 is an antibody to an HIV protein, so it may be theoretically possible for a standard antibody-based HIV diagnostic test to detect VRC01 for a short time period postinfusion or postinjection. This has not been observed in clinical studies to date.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling, or bleeding at the IV site and, rarely, infection, vein inflammation (phlebitis), or blood clot.

Risks of IV Infusion: The placement of an IV catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized through the use of aseptic techniques during product preparation and administration.

3 Objectives and endpoints

3.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in MSM+TG in North America, South America, and Switzerland

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in MSM+TG in North America, South America, and Switzerland

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

3.2 Secondary objectives and endpoints

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available post-HIV-infection serum samples

3.3 Exploratory objectives

Exploratory objective 1:

To assess use of FTC/TDF in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

4 Statistical considerations

4.1 Outline of the statistical considerations section

The statistical considerations section is organized as follows. Section 4.2 states the primary and secondary efficacy objectives in terms of the target prevention efficacy (PE) parameters that are estimated in the trial, and describes the hypothesis tests regarding these efficacy parameters. Section 4.4 summarizes a statistical rationale for using a 3-arm design, which adds to the scientific rationale provided in Section 2.4. Section 4.6 describes sample size and power considerations for the primary efficacy objectives, which justify the sample size of the trial. Section 4.6 also provides operating characteristics of the trial design for addressing the primary efficacy objective. Section 4.7 describes statistical power available for the secondary objective that compares PE between the two mAb dose groups. Section 4.8 describes statistical power available for detecting safety problems of the mAb in terms of SAEs. Section 4.9 summarizes the approach to monitoring the trial including interim analysis reports provided to the DSMB. Sections 4.10, 4.11, and 4.12 describe PrEP assessments, randomization, and blinding, respectively. Section 4.13 describes the approach to statistical analysis, ordered first by the approach to the analysis of PE, and secondly by the approach to the assessment of correlates of protection.

4.2 PE parameter for the primary analysis of prevention efficacy

Let PE denote the overall PE of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. This PE parameter is defined as

$$PE = [1 - \text{Cumul. incid. ratio (pooled mAb grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%,$$

where the cumulative incidence ratio is the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive the mAb divided by the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive control. PE is the target parameter for the primary analysis of overall PE.

The primary analysis tests the null hypothesis

$$H_0: PE = 0\% \text{ versus the alternative hypothesis } H_1: PE \neq 0\%$$

using a 2-sided alpha = 0.05 level test that accounts for sequential monitoring for potential harm, non-efficacy, and high efficacy.

4.2.1 Rationale for the PE parameter that measures prevention efficacy averaging over participant subgroups that access different elements of the HIV-1 prevention package

The primary PE parameter measures the efficacy of VRC01 averaging over the 10 mg/kg and 30 mg/kg subgroups, in the population-based context of study participants with different risk characteristics including host genetics, HIV-1 risk taking behaviors, and

participant decision to use different elements of the HIV-1 prevention package. The HIV-1 prevention package includes FTC/TDF PrEP, and is in harmony with the World Health Organization's November 2015 guideline on PrEP use that states "PrEP should be an additional prevention choice in a comprehensive package of services that also includes HIV testing, counseling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, voluntary medical male circumcision and harm reduction interventions for people who use drugs" [111]. The HIV-1 prevention package includes all of these elements, and study staff educate participants about the comprehensive package and facilitate access to and use of each measure. By conducting the study in a cohort of study participants who make the informed choice to use different elements of the package, the primary analysis result generalizes to a population with such heterogeneity of choice and aims to reflect efficacy in a real-world setting where such heterogeneity occurs. In particular, all study participants are counseled about the known high efficacy of FTC/TDF and are encouraged to take it. Because past experience and research has found that some individuals may prefer to not take FTC/TDF, the primary analysis conducted in a cohort reflecting such heterogeneity in prevention choices allows a representative population of individuals to participate in the trial. This approach also accommodates changes in prevention choices during the course of the trial, where the primary PE parameter is estimated in the context of these changes.

How many MSM/TG persons will initiate and adhere to fixed dose FTC/TDF when it is offered as part of an HIV prevention package is unclear; estimates vary considerably in the literature. Open label extensions of the PrEP clinical trials and reporting from the first demonstration projects of PrEP offer some insights into PrEP uptake and adherence in high risk MSM. As discussed in Section 2.5.1, uptake of PrEP has ranged from 76% in iPrEX OLE to 60% in the US-based Demo Project and 51% in PrEP Brasil [76,87,88]. While the uptake is substantial, from these studies it is also clear that a substantial fraction of high risk MSM will not initiate PrEP. Moreover, even in the context of intensive counseling, long-term adherence—especially adherence during periods of highest risk—is also unclear. It is thus most pertinent to advancing the science of HIV prevention to conduct the VRC01 primary PE analysis in a cohort reflecting heterogeneity in prevention choices, representative of the population at risk. This approach will also accommodate changes in prevention choices that emerge during the course of the trial, as the primary PE parameter will be estimated in the context of these changes.

4.3 PE parameters for secondary analyses of prevention efficacy

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall PE of the 10 mg/kg mAb group and let PE30 be the overall PE of the 30 mg/kg mAb group, defined as

$$PE_{10} = [1 - \text{Cumul. incid. ratio (mAb-10 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%$$

and

$$PE_{30} = [1 - \text{Cumul. incid. ratio (mAb-30 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%.$$

Secondary analyses test the null hypotheses

H0: PE10 = 0% versus the alternative hypothesis H1: PE10 $\neq$ 0%

and

H0: PE30 = 0% versus the alternative hypothesis H1: PE30 $\neq$ 0%

using 2-sided alpha = 0.05 level tests. Both unadjusted p-values and Holm-Bonferroni p-values will be reported for each of the individual dose versus placebo group analyses.

In addition, the following secondary analyses of PE are conducted:

- Assess a dose-response effect by testing the null hypothesis

H0: Cumul. HIV-1 incidence by 80 Wks equal in the 3 groups versus H1: $0\% \leq \text{PE}_{10} \leq \text{PE}_{30}$ with at least one strict inequality

- Test the complete null hypothesis that the HIV-1 incidence is the same in the three treatment groups versus the alternative hypothesis that there are some differences
- Test for different HIV-1 incidence between the two mAb groups, where a finding of PE30 significantly greater than PE10 would demonstrate that assignment to a higher mAb dose level causes higher PE

4.4 Statistical rationale for the 3-arm design compared to a 2-arm design

An alternative design would compare a single dose and schedule of the VRC01 mAb versus control. However, the 3-arm design allows addressing additional scientific questions and improves the assessment of correlates of protection, without requiring more participants by virtue of the primary analysis being based on the pooled mAb groups versus control. Specifically, consider a 2-arm design with 2:1 allocation to a single dose of VRC01 versus placebo, compared to the 3-arm design in the protocol with 1:1:1 allocation. For scenarios where the average of PE10 and PE30 equal PE set to a number greater than 0 and less than 1, power to reject H0: PE $\leq$ 0% in favor or H1: PE > 0% is very similar between the two trial designs, for the same total number of study participants. By providing results about estimated PE10 and estimated PE30 as well as about pooled estimated PE, the trial provides data for modeling of how PE would change given a new dose and/or schedule.

A second advantage of the 3-arm design is that it allows a direct assessment of the causal effect of different mAb infusion doses on HIV-1 incidence based on randomization of treatment assignments (a so-called 'group-level' correlate of protection), which can directly prove the concept that a higher mAb dose causes a greater level of protection. In contrast, with a 2-arm design the association between mAb marker characteristics and the level of PE can only be inferred with non-randomized epidemiological analysis approaches for which the results cannot be guaranteed to be free from postrandomization selection bias [112,113]. That is, without a randomization to multiple mAb interventions a result that a mAb characteristic is associated with reduced incidence of HIV-1 infection may not imply that mAb recipients with the characteristic have a higher level of PE. For instance, the implication may fail if participants tend to have fewer HIV-1 exposures during the few weeks after infusion visits compared to during the few weeks before infusion visits, which could possibly occur related to the counseling and informed consent process. Or, the implication may fail if the mAb characteristic marks an intrinsic

HIV-1 susceptibility factor that is not caused by administration of the mAb [114-116]. A third advantage of the 3-arm design is that the random assignment of two mAb doses creates greater inter-individual variability in mAb characteristics, which improves statistical power for the assessment of individual-level correlates of protection.

In sum, the dose-response 3-arm design has the advantages of allowing more insightful and rigorous inferences about causal effects of the mAb and greater resolution of correlates of protection, and allows addressing the additional question of whether a higher dose confers greater PE than a lower dose.

4.5 Use of safety run-in data in the analyses of prevention efficacy

Data from all participants, irrespective of enrollment into the safety run-in cohort, are included in analyses of prevention efficacy. This is valid because all enrolled participants have the same schedule for infusions and follow-up. In the event that infusions are paused, the analysis plan would be amended to censor participant follow-up more than approximately 10 weeks beyond the last infusion after the pause is instituted.

4.6 Sample size calculations for testing for overall PE (Primary objective 2)

The trial is designed to have 90% power to test

$H_0: PE \leq 0\%$ versus the alternative hypothesis $H_1: PE > 0\%$

if the level of overall pooled PE is 60% (with a 1-sided 0.025 α -level test); the design fits the paradigm of an intermediate-sized phase 2b screening efficacy trial proposed for HIV-1 vaccine efficacy trials by Rida, Fleming et al [117].

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing log-transformed cumulative incidences of HIV-1 infection by the Week 80 visit between randomized groups, in the presence of the sequential monitoring described below. Power is computed based on simulating 10,000 efficacy trials under assumptions described below using the R package seqDesign.

4.6.1 Assumptions of the sample size calculations including sequential monitoring for PE

The following assumptions are made for the sample size calculations:

- 10% annual dropout incidence in each of the three study groups
- 32 month uniform accrual with halved accrual during the first three months (approximating current accrual projections)
- visits every 4 weeks for HIV-1 diagnostic tests through Week 80 and HIV-1 status at Week 80 is known
- 3% annual HIV-1 incidence in the control group

- For each of the mAb treatment groups, average PE versus control within an 8-week infusion interval is assumed to be the same for each of the 10 infusion intervals
- Sequential monitoring of the mAb groups versus control to stop early for:
 - Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring adjusted 90% CI lying below 0%]
 - Non-efficacy [Establish that PE (pooled over the mAb groups) $\leq 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
 - High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

With the exception of the potential harm monitoring, the sequential monitoring of PE does not use critical values adjusted for the number of analyses. Examination of the design operating characteristics (reported in the figures and tables below) was used to ensure that this approach provides a fitting trade-off of the control of false negative and false positive error rates.

Justification for the incidence assumptions is provided in Section 4.6.6.

We also show power calculations allowing for lower levels of HIV-1 incidence or higher levels of dropout. In particular, we show power calculations assuming 1.65% annual HIV-1 incidence in the control group, which would account for lower than expected incidence rates due to increased PrEP usage. Similarly, power calculations based on 15% annual dropout incidence are also considered.

4.6.2 Power curves and operating characteristics of the design (Primary objective 2)

Required sample sizes to achieve 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of PE are determined based on 1-sided 0.025 level Wald tests as described above. The power calculations are repeated for a range of sample sizes to determine the required sample size to achieve 90% power as reported in Figure 4-1. These power calculations are conducted using the open source R package seqDesign developed by the protocol statisticians [118], which computes power based on simulating many thousands of efficacy trials, applying the sequential monitoring procedures to each trial, and computing power as the fraction of the trials where the 1-sided 0.025-level Wald test rejects the null hypothesis. The calculations are based on a large number of simulated efficacy trials.

Figure 4-1 shows the sample size per group in the three treatment groups required to have 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of $PE = PE_{10} = PE_{30}$. The results show that about $N = 2300$ total participants are needed to achieve 90% power to detect $PE = 60\%$; the sample size $N = 2700$ total participants (900 per arm) is selected to build in a provision of robustness to the control group annual incidence being lower than 3.0%. In particular, the lowest control group annual HIV-1 incidence to retain power of at least 90% to detect $PE = 60\%$ is 2.3%.

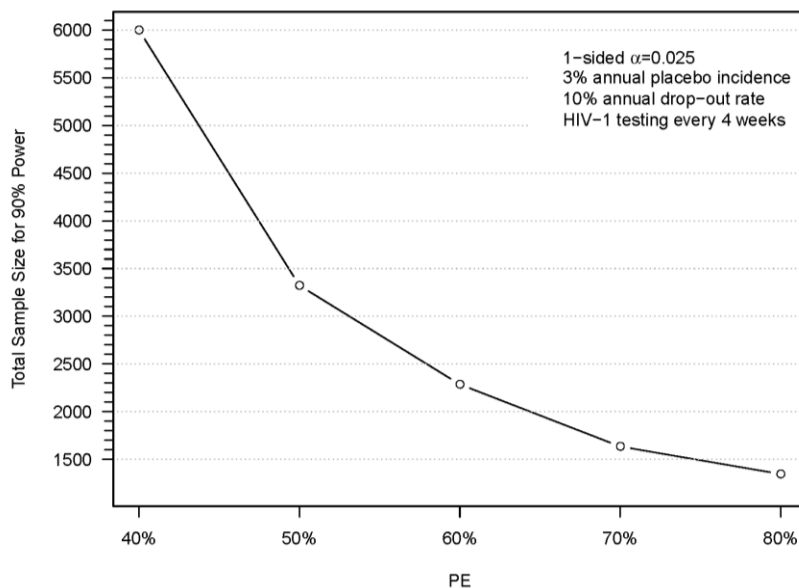


Figure 4-1 Total sample size for 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

Table 4-1 shows power available to reject the null hypothesis under different levels of true PE.

**Table 4-1 Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ under different effect sizes
 $PE = PE_{10} = PE_{30}$**

	Unconditional Power ($\times 100$)
0%	2.4
10%	7.8
20%	19.0
30%	38.6
40%	62.9
50%	84.2
60%	96.0
70%	99.5
80%	>99.9
90%	>99.9
95%	>99.9

The power calculations for the primary analysis of prevention efficacy were done assuming $PE_{10} = PE_{30}$, and it is of importance to also understand power available in the primary analysis in the event that PE_{10} differs from PE_{30} . Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ when PE equals a fixed constant PE_0 greater than 0 and less than 1 is very similar for different values of (PE_{10}, PE_{30}) subject to the constraint of average value $(PE_{10} + PE_{30})/2 = PE_0$. For example, power to test H_0 vs. H_1 is very similar for $(PE_{10}, PE_{30}) = (60\%, 60\%)$ and for $(PE_{10}, PE_{30}) = (30\%, 90\%)$. This result attains because all of these scenarios have the same number of expected HIV-1 infection events among study participants assigned to receive VRC01. Power tends to be slightly greater for differential scenarios like $(PE_{10}, PE_{30}) = (30\%, 90\%)$ compared to the equal scenario $(PE_{10}, PE_{30}) = (60\%, 60\%)$, because the hypothesis testing procedure stratifies by VRC01 dose group, gaining efficiency by accounting for a baseline variable that predicts HIV infection. Therefore, the trial is powered to detect the design alternative

of a dose-pooled VRC01 efficacy PE equal to 60%, regardless of whether VRC01 efficacy differs by dose group.

4.6.3 Additional operating characteristics of the design for assessing primary objective 2

For the selected sample size ($N = 2700$), Figure 4-2 shows the power curves for rejecting $H_0: PE \leq 0\%$ in favor of $H_0: PE > 0\%$ for a range of fixed values of the pooled PE. The power for rejecting H_0 when the HIV-1 incidence rate is lower than projected or dropout rate is higher than projected are included in the figure.

The scenario of 1.65% annual HIV-1 incidence represents various amounts of PrEP use among study participants. In particular, this 1.65% assumption is attained if 50% of person-years at-risk are not during PrEP use with annual incidence of 3.0%, and the other 50% of person-years at-risk are during PrEP use at PrEP efficacy of 90% and hence with annual incidence of 0.3% [$1.65\% = (3.0\% + 0.3\%)/2$]. In addition, a slightly higher control group annual incidence of 2.0% is attained under each of the following three scenarios, all of which assume 90% PrEP efficacy during PrEP use and 3% annual HIV-1 incidence during person-years at-risk without PrEP use: (A) 50% of person-years at-risk during PrEP use in the U.S. and Switzerland; 25% in Peru and Brazil; and 69% participants enrolled in the U.S. and Switzerland; (B) 60% of person-years at-risk during PrEP use in the U.S., 30% in Peru and Brazil, and 61% of participants enrolled in the U.S. and Switzerland; (C) 75% of person-years at-risk during PrEP use in the U.S. and Switzerland, 40% in Peru and Brazil, and 48% of participants enrolled in the U.S. and Switzerland. These calculations support that the study has adequate power to meet the primary efficacy objective if there is substantial PrEP use.

Moreover, we also conducted power calculations assuming 50% of person-years at-risk during PrEP use in all three countries, which means that the overall annual HIV-1 incidence in the placebo group is 1.65% [$= (3.0\% + 0.3\%)/2$]. In this scenario, the trial has 78% power to detect $PE = 60\%$.

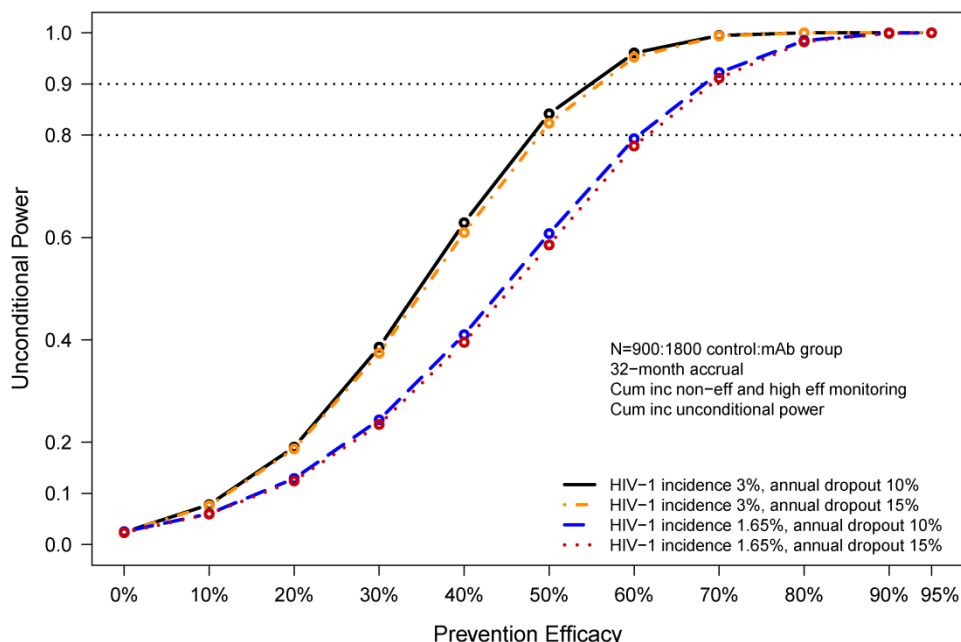


Figure 4-2 Unconditional power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for a range of fixed values of pooled PE based on primary assumptions for HIV-1 incidence and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.6.4 Additional operating characteristics of the primary analysis accounting for the sequential monitoring

For the selected sample size ($N = 2700$), Figure 4-3 shows probabilities of reaching each possible trial monitoring outcome, pooling over the two mAb treatments (under the primary assumptions about HIV-1 incidence and dropout rates). More specifically, the monitoring outcomes include potential harm, non-efficacy, and high efficacy. Table 4-2 provides the same information in tabular form. In addition, the figure and table show unconditional power in the primary analysis to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$.

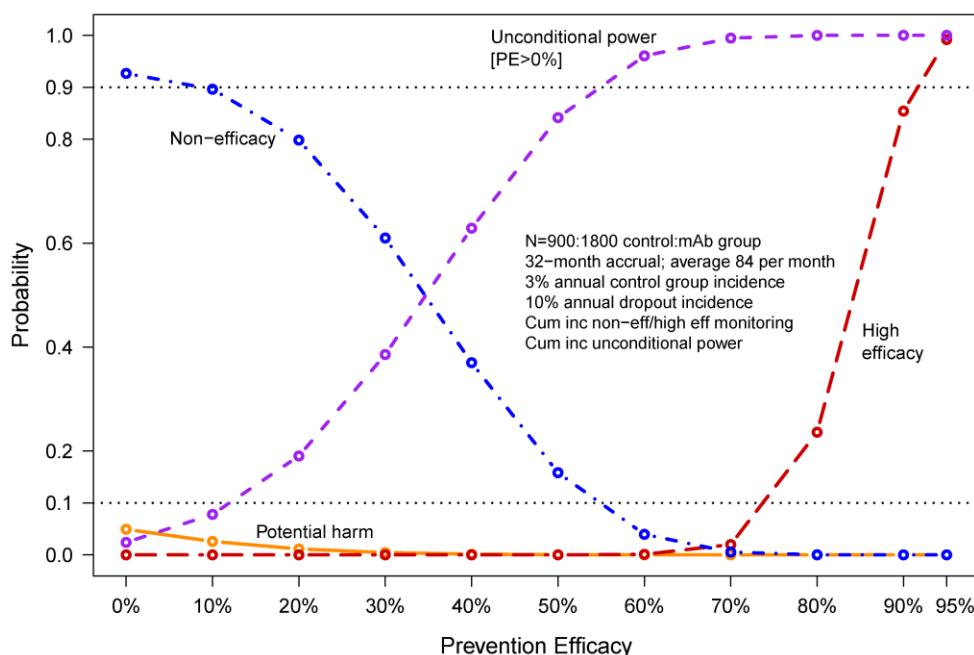


Figure 4-3 Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the primary null hypothesis $H_0: PE \leq 0\%$ with 900 control recipients and 1800 mAb recipients (1-sided 0.025-level tests)

Table 4-2 Probabilities (x 100) of reaching each possible trial monitoring outcome, and unconditional power (x 100) to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$, pooling over the two mAb groups (1-sided 0.025-level tests)

PE	HR	Weed Out at Interim Analysis			Unconditional Power PE > 0%
		Potential Harm PE < 0%	Non-Efficacy PE < 40%	High Efficacy PE > 70%	
	3.0	95.3	4.7	0.0	0.0
	2.5	87.8	12.2	0.0	0.0
	2.0	69.1	30.9	0.0	0.0
	1.5	34.0	66.0	0.0	0.0
0%	1.0	4.9	92.7	0.0	2.4
10%	0.9	2.6	89.6	0.0	7.8
20%	0.8	1.1	79.8	0.0	19.0
30%	0.7	0.4	61.0	0.0	38.6
40%	0.6	0.1	37.0	0.0	62.9
50%	0.5	0.0	15.8	0.0	84.2
60%	0.4	0.0	4.0	0.1	96.0
70%	0.3	0.0	0.5	2.0	99.5
80%	0.2	0.0	0.0	23.6	100.0
90%	0.1	0.0	0.0	85.4	100.0
95%	0.0	0.0	0.0	99.2	100.0

N = 900:1800 Control:mAb group
 3% annual incidence in the Control group
 10% annual dropout
 Cumulative incidence-based non-efficacy monitoring
 Cumulative incidence-based high-efficacy monitoring
 Cumulative incidence-based unconditional power

Table 4-3 shows the numbers of HIV-1 infection endpoints during the trial expected under the null hypothesis scenario $PE = PE_{10} = PE_{30} = 0\%$ and under the design

alternative hypothesis scenario $PE = PE_{10} = PE_{30} = 60\%$. Under the design alternative hypothesis scenario, the calculations show that 37 HIV-1 infection endpoints are expected in the control group and 30 HIV-1 infection endpoints are expected in the two mAb groups combined after 80 weeks of follow-up.

Table 4-3 Cumulative number of HIV-1 infection endpoints over 80 weeks of follow-up under the null hypothesis scenario $PE_{10} = PE_{30} = 0\%$ and under the design alternative hypothesis scenario $PE = PE_{10} = PE_{30} = 60\%$. Medians are computed based on simulating a large number of efficacy trials.

PE₁₀ = PE₃₀	Weeks since first person in	Median number of control endpoints	Median number of pooled mAb group endpoints
0%	0	0	0
0%	26	0	1
0%	52	3	7
0%	78	9	18
0%	104	16	32
0%	130	22	45
0%	156	25	50
0%	182	26	54
0%	208	26	55
0%	210	26	55
60%	0	0	0
60%	26	0	0
60%	52	3	3
60%	78	9	7
60%	104	16	13
60%	130	23	19
60%	156	30	24
60%	182	35	28
60%	208	37	30
60%	219	37	30

4.6.5 Power curves for secondary hypothesis tests about PE in each mAb group

Figure 4-4 shows unconditional power to reject the null hypothesis $H_0: PE_{10} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{10} > 0\%$ (or, equivalently, the null hypothesis $H_0: PE_{30} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{30} > 0\%$), where PE_{10} and PE_{30} measure prevention efficacy in each mAb group separately.

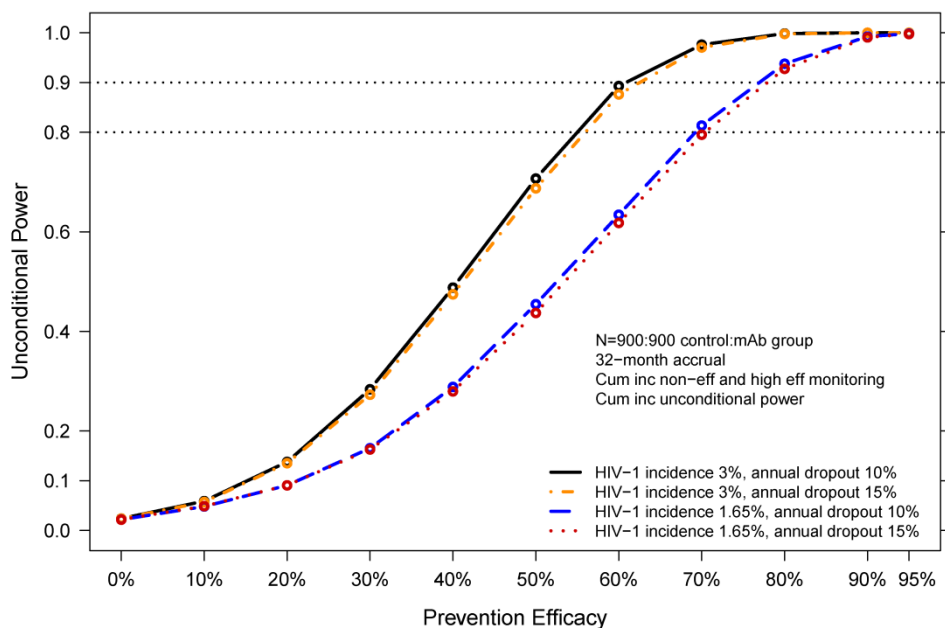


Figure 4-4 Unconditional power to reject $H_0: PE_{10} \leq 0\%$ in favor of $H_1: PE_{10} > 0\%$ (or $H_0: PE_{30} \leq 0\%$ in favor of $H_1: PE_{30} > 0\%$) based on primary assumptions about HIV-1 incidence rate and dropout rate (1-sided 0.025-level tests). Power curves are also shown for lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.6.6 Rationale for the HIV-1 incidence assumptions

The assumption of 3% annual HIV-1 incidence in the control group accommodates background PrEP use by assuming incidence is decreased by two parameters: (1) the fraction of person-years at-risk during which PrEP is used; and (2) the level of efficacy of PrEP during PrEP use. Figure 4-5 shows the annual HIV-1 incidence in the control group as a function of these two factors, for a scenario where the annual HIV-1 incidence is 4% in the absence of any PrEP use. Based on HVTN 505 data (US participants only) through September 30, 2014, the annual HIV-1 incidence in the control group was 2.0% (95% CI 1.5%–2.7%) and in the vaccine and control groups pooled was 2.1% (95% CI 1.5%–2.8%). From HVTN 505, based upon case report form (CRF) collection of PEP/PrEP med usage and responses to questions regarding usage posed on the ‘anonymous’ (to the site) ACASI questionnaire through June 1, 2014, 5% of participants reported ever using PrEP. In HVTN 505 the amount of person-years at risk during periods of PrEP use was likely well below 5%, and, therefore, the 2.1% annual incidence is a reasonable assumption for the baseline rate without PrEP. In particular, assuming 1.6% annual control incidence in the US and Switzerland (which is expected if 27% of person-years at risk are during PrEP use and PrEP efficacy is 90% during use) and assuming 5% annual control incidence in South American participants [7], (with 5% of person-years at risk during PrEP use and 90% PrEP efficacy during use), 44% of participants enrolled at South American sites would yield the assumed 3% annual control incidence rate.

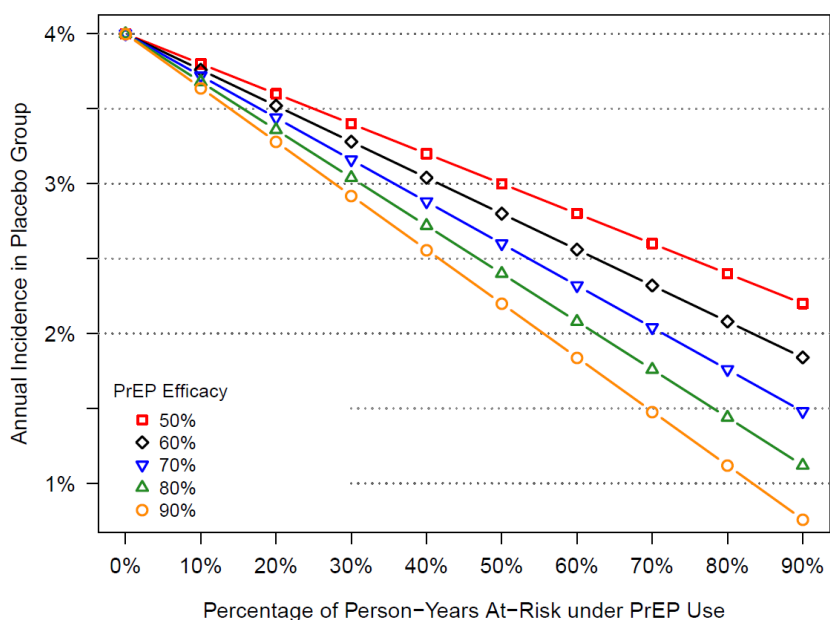


Figure 4-5 Annual HIV-1 incidence in the control group assuming 4% annual HIV-1 incidence in the hypothetical scenario of no PrEP use, under different levels of PrEP use and levels of PrEP efficacy

Higher than expected use of PrEP would be reflected in lower than expected annual incidence rates, as shown in Figure 4-5. As shown in Figure 4-2, the trial would still provide enough statistical information to be powered to detect highly relevant prevention efficacy effect sizes if annual incidence rates are lower than we have estimated here due to higher than expected use of PrEP.

4.7 Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group

Table 4-4 reports power calculations for comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. The calculations assume the scenarios for true values of PE10 and PE30 indicated in the first two columns of the table. The results show that the study is well-powered to detect large differences, for example, with about 87% power to discriminate 30% vs. 80% PE and 40% vs. 85% PE, but may miss moderate differences (e.g., 34% power to discriminate 30% vs. 60% PE). In contrast, the study has high power to correctly select the best mAb dose group given moderate efficacy differences. Specifically, if the true PE30 is moderately greater than the true PE10, then there is high probability that the estimated PE30 would be greater than the estimated PE10, such that the 30 mg/kg mAb dose group would be selected.

Table 4-4 Statistical power for comparing the 10 versus 30 mg/kg mAb groups: Power to correctly rank-and-select the best mAb group and power to detect superiority of the 30 mg/kg mAb group over the 10 mg/kg mAb group in a head-to-head comparison

PE10	PE30	Power to Rank-and-Select Best mAb Dose Group [§]	Power to Detect PE10 Different from PE30 [#]
20%	60%	88.3	58.3
30%	60%	86.7	39.5
40%	60%	81.7	21.6
20%	70%	97.2	83.7
30%	70%	96.8	69.4
30%	80%	99.8	91.5
40%	85%	>99.9	90.8
50%	85%	99.7	77.0

[§] Probability that the mAb dose group that is truly better (the 30 mg/kg dose group in the scenarios considered in the table) is correctly selected based on the point estimate for PE30 exceeding that for PE10. Specifically, correct selection entails that the estimated PE30 is greater than the estimated PE10 and PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

[#] Cumulative hazard-based 2-sided Wald tests comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. Rejection of the null hypothesis requires that PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

4.8 Sample size calculations for safety

We consider the statistical power of Fisher's exact test to detect a higher rate of SAEs in a mAb group (Group 1 or 2 with $n = 900$ participants) versus the control group (Group 3 with $n = 900$). Based on HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE. The tests use a 2-sided α -level of 0.05. This level does not correct for the 4 comparisons; however, this is appropriate because it is desirable to maximize power to detect a safety problem. For the safety calculations, we assume no missing data as almost all participants will have some follow-up data for safety.

To describe the precision of the study to characterize differences in SAE rates between groups, Table 4-5 shows 2-sided 95% CIs for different levels of observed differences (mAb group-control) of event rates between a mAb group of size $n_1 = 900$ (or the combined mAb groups $n_2 = 1800$) and a control group of size $n_0 = 900$. For example, an observed rate difference of 6% between the combined mAb groups and control group will lie between 3.5% and 8.7% with 95% confidence, when the observed event rate in the control group is 4%.

Table 4-5 Two-sided 95% CIs for different observed event rate differences of safety endpoints between the mAb recipient and control groups*

Observed event rate in controls (n0 = 900)	Observed event rate in a single mAb group (n1 = 900)	Observed event rate in combined mAb groups (n2 = 1800)	Rate difference (mAb group – control)	95 % CI (n1 = 900)	95% CI (n2 = 1800)
0/900 = 0%	0/900 = 0%	0/1800 = 0%	0%	(-0.0050, 0.0050)	(-0.0050, 0.0022)
	18/900 = 2%	36/1800 = 2%	2%	(0.0125, 0.0317)	(0.0143, 0.0278)
	36/900 = 4%	72/1800 = 4%	4%	(0.0289, 0.0550)	(0.0317, 0.0503)
	90/900 = 10%	180/1800 = 10%	10%	(0.0817, 0.1217)	(0.0869, 0.1150)
	180/900 = 20%	360/1800 = 20%	20%	(0.1750, 0.2279)	(0.1819, 0.2192)
18/900 = 2%	0/900 = 0%	0/1800 = 0%	-2%	(-0.0317, -0.0125)	(-0.0317, -0.0125)
	16/900 = 2%	36/1800 = 2%	0%	(-0.0136, 0.0136)	(-0.0127, 0.0106)
	32/900 = 4%	72/1800 = 4%	2%	(0.0041, 0.0369)	(0.0060, 0.0327)
	80/900 = 10%	180/1800 = 10%	8%	(0.0592, 0.1030)	(0.0631, 0.0968)
	160/900 = 20%	360/1800 = 20%	18%	(0.1531, 0.2088)	(0.1594, 0.2009)
36/900 = 4%	0/900 = 0%	0/1800 = 0%	-4%	(-0.0550, -0.0289)	(-0.0550, -0.0289)
	18/900 = 2%	36/1800 = 2%	-2 %	(-0.0369, -0.0041)	(-0.0360, -0.0067)
	36/900 = 4%	72/1800 = 4%	0%	(-0.0188, 0.0186)	(-0.0170, 0.0150)
	90/900 = 10%	180/1800 = 10%	6%	(0.0369, 0.0842)	(0.0405, 0.0787)
	180/900 = 20%	360/1800 = 20%	16%	(0.1314, 0.1899)	(0.1372, 0.1826)

*95% CIs are computed using the method of Berger and Boos [119].

Figure 4-6 shows the power to detect an elevated SAE rate as a function of the true rate in the mAb group under consideration.

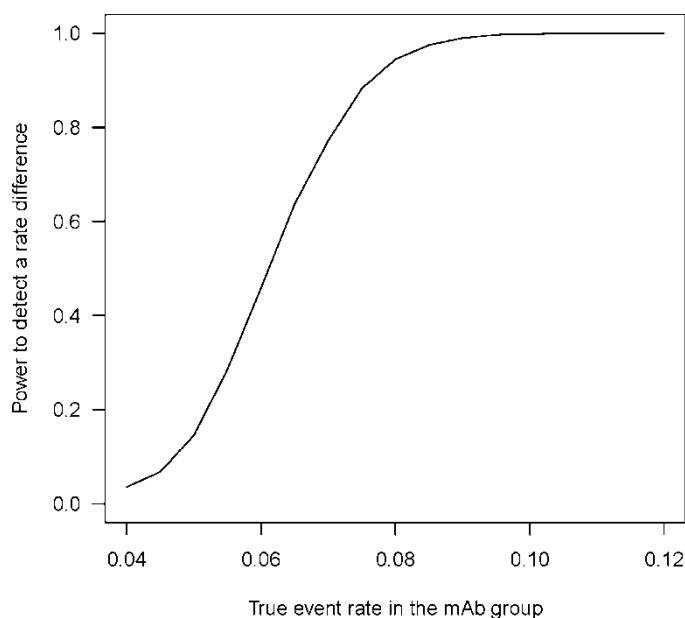


Figure 4-6 Power to detect a greater SAE rate in a mAb group (n = 1800) versus the control group (n = 900) given a 4% SAE rate in the control group (2-sided 0.05-level test)

Figure 4-6 shows that there is 80% power to detect a higher SAE rate in a mAb arm if the true SAE rate is 7.1% and 90% power if the true rate is 7.6%.

4.9 Monitoring of the trial

4.9.1 Role of the Data Safety Monitoring Board (DSMB)

The study DSMB will review study data at 6-monthly interim analyses to evaluate safety, integrity, and efficacy of the ongoing trial. Following each DSMB meeting, the DSMB reports to the Oversight Committee (OC) a summary of the trial review, which may include recommendations to modify or terminate the trial. The DSMB is guided by a trial monitoring plan, and reviews and approves the monitoring plan before the trial initiates.

Each 6-monthly DSMB report will include a complete analysis of safety data. If a total of $N = 20$ participants reach the Week 12 study visit before the first DSMB report is generated, then a safety report based on these data will be provided to the DSMB as soon as possible and before the first DSMB meeting. The contents of the early report are the same as the contents in the scheduled 6-monthly DSMB reports.

In addition, as soon as 10 grade 2 or higher AEs occur, a report will be generated describing these AEs and will be provided to the DSMB. The DSMB reports will also tabulate occurrence of SAEs, and of AEs judged related to product, accounting for the number of infusions received.

4.9.1.1 Sequential monitoring for potential harm, non-efficacy, and high efficacy

The trial uses sequential monitoring of the mAb groups versus control to stop early for:

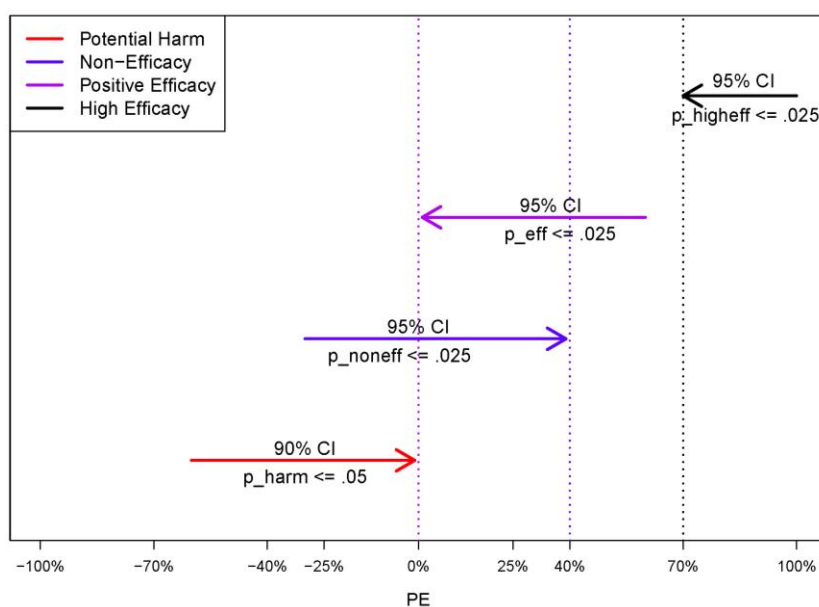
- Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring-adjusted 90% CI lying below 0%]
- Non-efficacy [Establish that PE (pooled over the mAb groups) $< 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
- High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

The sequential monitoring is based on CIs in order that the result of the study that would be reported would convey evidence supporting the conclusion of potential harm, non-efficacy, or high efficacy. Freidlin, Korn, and Gray [120] discuss a rationale for this approach to non-efficacy monitoring. The sequential monitoring for potential harm is based on monitoring-adjusted 1-sided 0.05-level tests (instead of 1-sided 0.025-level tests) for prudence to protect the safety of study participants (ie, less precision is required to meet a guideline for potential harm than to meet guidelines for non-efficacy or high-efficacy). Once non-efficacy monitoring commences, the potential harm monitoring after each infection ceases, as the non-efficacy monitoring now provides the function of detecting an elevated rate of HIV-1 infection. The non-efficacy monitoring is supplemented with conditional power calculations that report estimates of the probability of rejecting the null hypothesis of zero PE under different assumptions about the estimated PE if the trial were to continue to the end. The sequential monitoring plan is summarized in Table 4-6 and Figure 4-7.

Table 4-6 Summary of sequential monitoring of PE

Monitoring Type	Hypotheses	Testing Approach	Size of Test	Stopping Boundary	Timing of Interim Analyses
Potential Harm	H0: PE $\geq$ 0% vs H1: PE < 0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the mAb	Specified in the monitoring plan	Near-constant 1-sided p-value cut-off controlling the FWER at $\alpha = 0.05^*$	After every infection from 20 th total until first non-efficacy analysis
Non-Efficacy	H0: PE $\geq$ 40% vs H1: PE < 40%	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI below 40% supplemented with conditional power (specified in the monitoring plan)	6-monthly starting based on an event-driven trigger specified in the monitoring plan
High Efficacy	H0: PE $\leq$ 70% vs H1: PE > 70%	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI above 70%	6-monthly starting at the same time as for non-efficacy

* Equivalently, a monitoring-adjusted 2-sided 90% CI based on inversion of the test statistic lies below 0%. The 1-sided p-value significance threshold stopping boundaries after each infection event are specified in the study monitoring plan.

**Figure 4-7 Stopping boundaries for the sequential monitoring based on 2-sided CIs (or on the corresponding 1-sided p values)**

Details of the sequential monitoring plan will be provided in a separate trial monitoring plan. The sequential monitoring is closely related to what was done for the HVTN 505 HIV-1 vaccine efficacy trial [121] (background discussion in [74]).

4.9.2 Feasibility check and guideline for continuing enrollment as planned

In addition to the sequential monitoring of PE, feasibility monitoring is done for the first 120 enrolled participants. This feasibility monitoring is based on the first four 8-week intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of participants attend clinical visits and receive the infusions per the protocol. The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) supplemented by data on visit attendance, which corresponds to adherence to receipt of infusions. Additional details will be provided in the trial monitoring plan.

The feasibility monitoring based on the first 120 enrolled participants will use the following guideline for continuing enrollment as planned: continued participation by the Week 32 visit pooled over the 3 groups is greater than 80%.

If the blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is warranted.

4.9.3 Monitoring for futility to assess PE

The objective of monitoring the trial for futility to assess PE is to monitor progress toward the minimum needed target number of treatment arm-pooled HIV-1 primary endpoint infections by the Week 80 visit in the MITT cohort. Two targets are monitored for:

1. the total number of HIV-1 infections needed to achieve the planned 90% power to detect PE = 60%, and
2. the total number of HIV-1 infections needed to achieve 65% power to detect PE = 60%,

each using a 1-sided 0.025-level Wald test of $H_0: PE \leq 0\%$ against $H_1: PE > 0\%$, assuming proportional hazards of HIV-1 infection in the pooled VRC01 and control groups. The target numbers in (1) and (2) are 56 and 29, respectively (calculated by solving equation (1) in Schoenfeld [122]). The rationale for considering the two targets is as follows: (i) if the trial cannot achieve the planned 90% power to detect PE = 60%, considerations about enrollment modification or expansion are warranted, and (ii) if the trial cannot achieve even 65% power to detect PE = 60%, considerations about completing the trial early for futility to assess PE are warranted.

Two versions of the futility monitoring report will be generated. A report provided to the DSMB will be included in 6-monthly closed DSMB reports, starting in April 2018, and will report:

- a. the estimated distribution of the total (i.e., treatment arm-pooled) number of HIV-1 infections, with corresponding power to reject $H_0: PE \leq 0\%$ using a 1-sided 0.025-level Wald test under the alternative hypothesis PE = 60% throughout the trial,
- b. the estimated probability that the total number of HIV-1 infections is ≥ 56 (target 1) with 95% credible intervals,
- c. the estimated probability that the total number of HIV-1 infections is ≥ 29 (target 2) with 95% credible intervals,
- d. the estimated distribution of the number of HIV-1 infections in each of the three treatment arms.

The distributions in (a) and (d) will also be summarized by the mean number of HIV-1 infections with a Wald 95% confidence interval. The estimation procedure for (a)–(d) will be conducted under each of the following two scenarios:

- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 60% (the design alternative), and
- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 0% (the null hypothesis).

The reason for conducting the estimation procedure twice is that the purpose of the results for the 56 endpoint target (b) is to trigger considerations for trial modifications, whereas the purpose of the results for (c) is to trigger considerations for early trial completion due to futility, where it is desired to reach the guideline (b) more easily/readily than the guideline (c). Accordingly, the results for (b) are interpreted focusing on the prior of PE = 60%, which makes it more likely to reach a guideline than the prior of PE = 0%, and the results for the 29 endpoint target (c) are interpreted focusing on the prior of PE = 0%, which makes it less likely to reach a guideline than the prior of PE = 60%.

Furthermore, a treatment-blinded report will be generated for distribution to the OC after each DSMB meeting takes place and will report estimates listed in (a)–(c) above calculated based only on treatment-blinded data. The reported results pertaining to estimates (a)–(c) will be identical to those in the DSMB report.

While it is the primary responsibility of the OC to make decisions regarding trial operations and modifications based on the monitoring of treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. More specifically, the DSMB can evaluate the progress toward primary endpoint targets in the context of the treatment-unblinded data, and based on this review may recommend to the OC to complete the trial early due to reaching a guideline for futility to assess PE (specified below).

The monitoring for futility to assess PE includes the following guidelines for trial modifications:

- **[Guideline for enrollment modifications]** If, in the PE = 60% scenario for the prior distribution, the estimated probability of reaching 56 total infections is less than 25%, the OC may consider enrollment modifications with the intention to be able to conduct the primary PE analysis with adequate power.
- **[Guideline for futility]** If, in the PE = 0% scenario for the prior distribution, the estimated probability of reaching 29 total infections is less than 25%, the DSMB may recommend completing the trial early based on the inability to conduct the primary PE analysis with adequate power. However, since this is a proof-of-concept trial, a high bar is desired for completing the trial early for futility, and therefore if this event occurs yet the non-efficacy monitoring has not started or the non-efficacy boundary has not been reached, then this guideline for futility also requires that the estimated PE for the pooled VRC01 vs. control arm is < 30% and the estimated PE for the VRC01 30 mg/kg vs. control arm is < 30%.

If enrollment is incomplete at the time of an interim futility analysis, then the outlined estimation procedures will use the average observed enrollment rate in approximately the

last 6 months for generating future enrollment data. In addition, a Bayesian approach will be used for generating future HIV-1 incidence data, conditional on observed data to-date. More specifically, the estimates in (a)–(c) will condition on the observed to-date treatment arm-pooled HIV-1 incidence rate, whereas the estimates in (d) will condition on the observed to-date (three) treatment arm-specific HIV-1 incidence rates. All estimates in (a)–(d) will also use the observed to-date treatment arm-pooled dropout rate for generating future dropout data.

If, at any time, these guidelines for futility to assess PE are met and yet it appears that value exists in continuing the trial, the statisticians will provide the DSMB and the OC with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

4.10 Assessment of PrEP use

The use of oral FTC/TDF as PrEP (either off-study or provided in the study) may impact study outcomes (eg, by lowering HIV incidence with a loss of study power). Dried blood spot samples will be collected and stored for assessment of quantitative concentrations of intracellular tenofovir (TFV) (see Section 9.6). A detailed testing plan, specified in the study monitoring plan, has been developed to prospectively monitor FTC/TDF use during the trial to inform the DSMB, and assess the potential impact of FTC/TDF use on PE of the study product. This plan employs testing samples from a calendar-based selection of visits that will ensure representative sampling of participants across the entire visit schedule at all sites throughout the study. Prevalence of PrEP will be reported both as the estimated proportion of participant visits with highly adherent PrEP use (above the concentration of TFV designated as consistent with daily dosing) and the proportion of participant visits with any detectable PrEP use (concentration of TFV above the lower limit of detection for the dried blood spot assay). Additionally, we will use knowledge of PK quantitative levels to estimate the proportion of study person years protected by highly adherent use of FTC/TDF. PrEP use measures will be reported by arm to the DSMB; in addition both the OC and the protocol team leadership will see pooled estimates of FTC/TDF use.

4.11 Randomization

The randomization sequence will be obtained by computer-generated random numbers and provided to each CRS through a Web-based randomization system. The randomization will be done in blocks to ensure balance across arms. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the SSP).

4.12 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know this information in order to ensure proper trial conduct. Any

discussion of study product assignment between pharmacy staff and any other CRS staff is prohibited.

When a participant leaves the trial prior to study completion, the participant will be told he or she must wait until all participants are unblinded to learn his or her treatment assignment.

Emergency unblinding decisions will be made by the site investigator. If time permits, the HVTN 704/HPTN 085 PSRT should be consulted before emergency unblinding occurs.

4.13 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many infusions they received. In the rare instance that a participant receives the wrong treatment at a specific infusion visit, the Statistical Analysis Plan will address how to analyze the participant's safety data. Analyses are modified intent-to-treat (MITT) in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected.

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

4.13.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, efficacy, and markers of mAb characteristics for primary- and secondary-objective analyses.

4.13.2 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

4.13.3 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first infusion, all participants will have received at least 1 infusion and therefore will provide some safety data.

4.13.3.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

4.13.3.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

4.13.3.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section 10.2.2) will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

4.13.3.4 Reasons for infusion discontinuation and early study termination

The number and percentage of participants who discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

4.13.4 Efficacy analysis

4.13.4.1 General approach

For the statistical analysis of prevention efficacy, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Given that all or almost all participants will receive the first infusion, the analyses are MITT, where all participants HIV-1 negative at entry receiving the initial infusion are included in the analysis, participants are analyzed according to their randomized treatment assignment, and participants retrospectively determined to be HIV-1 infected at entry based on treatment blinded procedures are excluded from the analysis. Additional analyses may be performed, limited to participants who received most or all infusions per protocol.

Cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms will be estimated by a transformation of Nelson-Aalen estimators [123] for the respective cumulative hazard functions of HIV-1 infection. PE parameters

will be estimated by one minus the ratio (mAb/control group) of these cumulative incidence estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported. These procedures will be used to test the hypotheses listed in Section 4.2.

As a supportive analysis for the hypotheses listed in Section 4.2, targeted maximum likelihood estimation (tMLE) will be used to estimate cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms [124,125]. The Statistical Analysis Plan will describe the details of implementation of the tMLE estimators in an automated and objective fashion. PE parameters will be estimated by 1 minus the ratio (mAb group/control) of these tMLE estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of HIV-1 infection over time, complementary secondary analyses will assess hazard-ratio based prevention efficacy using Cox proportional hazards models with score tests stratified by VRC01 dose group for testing whether prevention efficacy differs from zero. This analysis uses as the failure time the time from the most recent infusion to the estimated date of HIV infection, entered in the Cox model as a time-dependent covariate. This analysis can have increased power to detect prevention efficacy compared to the primary analysis of the cumulative incidence based parameter PE, if instantaneous prevention efficacy is higher when VRC01 concentrations are lower. Goodness-of-fit diagnostics will be applied to assess veracity of the proportional hazards assumption. The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity of the primary analysis does not depend on the proportional hazards assumption. The Cox model will also be used for a secondary analysis of PE in subgroups defined by the level of cumulative infusion adherence over time included in the model as a time-varying covariate.

Sensitivity analyses of the primary analysis will test $H_0: PE = 0\%$ with a log-rank test and with a Gehan-Wilcoxon test stratified by VRC01 dose group. To explore potential time-variations in prevention efficacy, instantaneous prevention efficacy over time defined based on the instantaneous hazard ratio (VRC01 vs. placebo) will be estimated with pointwise and simultaneous confidence bands using nonparametric kernel smoothing [126].

4.13.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety or efficacy endpoint assessments.

4.13.6 Specific approach for assessing PE, PE10, PE30

Primary objective 2 is addressed based on comparing cumulative HIV-1 incidence between the group of participants assigned to receive the VRC01 mAb (at either dose pooling over the two doses) and the group of participants assigned to the control group, and secondarily between each individual mAb dose group and the control group. For each prevention efficacy parameter PE, PE10 and PE30, point and 2-sided 95% CI estimates will be reported, along with the 2-sided p-values for testing the respective null hypotheses

(with 2-sided $p = 0.05$ the threshold for a significant effect). Unadjusted and Holm-Bonferroni p -values will be reported for testing of the secondary endpoint efficacy parameters PE10 and PE30.

4.13.7 Assessment of individual-level markers of VRC01 mAb that correlate with protection against HIV infections (Secondary objective 1)

Secondary objective 1 is addressed based on the measurement of VRC01 mAb markers over time in mAb group breakthrough HIV-1–infected cases and in a random sample of HIV-1–uninfected mAb group participants (marker subset), integrated with the genotypic and phenotypic sieve analysis of breakthrough HIV-1 viruses accounting for knowledge of the VRC01 antibody footprint. The main analyses of the secondary objective 1 pool over the two mAb doses to maximize statistical power.

The design and results requirements for successful identification of correlates of protection in secondary objective 1 are:

1. Sufficient sample size to observe enough participants diagnosed with incident HIV-1 infection during the primary follow-up period of 80 weeks postenrollment in the mAb arms
2. A result of significant beneficial overall mAb PE > 0%
3. Sufficiently frequent HIV-1 testing schedule and accurate HIV-1 diagnostics
4. Wide variability in the concentration and effector functions of the mAb over time and/or individuals, and the ability to measure these characteristics such that their timing relative to the timing of HIV-1 acquisition is estimated with adequately low measurement error
5. mAb marker sampling design that allows sufficiently accurate PK modeling of mAb characteristics over time

Note that the serum concentration mAb markers (secondary endpoints 2) are defined without reference to a particular HIV-1 Env sequence. The effector function markers (also secondary endpoints 2) are relative to specific HIV-1 Envs or panels of Envs, and thus may be linked to immunogenicity endpoints (and the antigen reagents for those endpoints) that would be used in future trials of candidate HIV-1 vaccines. Correlates of protection analyses directly assess how mAb PE depends on markers.

4.13.7.1 Sampling of mAb markers

Characteristics of the mAb or immune responses to the mAb are measured in participants assigned to the mAb treatment groups, and in a small number of participants assigned to the control group. The sampling design determining the set of participants for measuring the markers will be finalized after the primary analysis results. This sampling design will include measuring the markers in all mAb group primary endpoint cases with a minimal number of samples available prior to diagnosis of HIV-1 infection, and on a random sample of participants from each mAb group who complete follow-up to the Week 96 visit HIV-1 negative (mAb group control participants). The random sample of HIV-1 uninfected controls is chosen to create a common control:case ratio across participant strata defined by factors such as dose group, infusion adherence, and calendar period of

enrollment. For participants assigned to the control group, a smaller number of cases and HIV-1 negative controls will be sampled for measurement of markers. The timing of marker measurements is as follows:

- mAb group and control group cases: visits every 4 weeks up until the time of HIV-1 diagnosis and Day 61 (5 days post second infusion) if before diagnosis, plus the first positive visit and additional time-points post HIV-1 infection
- mAb group and control group marker subset controls: visits every 4 weeks through Week 80 plus Day 61 and Weeks 88 and 96

The Day 5 post-second infusion visit is included because it occurs shortly after the end of the distributive phase of the mAb, which together with the samples drawn just before infusions (Week 0, 8, ..., 72), the samples drawn 4 weeks post-infusions (Week 4, 12, ..., 76), and the Week 80, 88, and 96 samples 8–24 weeks post last infusion constitute the basis for modeling marker curves over time.

4.13.7.2 Overview of the analysis of a mAb marker as a correlate of protection

A correlates of protection statistical analysis plan will be finalized not using any information on case-control status of participants; this plan will contain details of the statistical analysis. We provide a brief summary here. For a given mAb recipient, let $S(t)$ be a marker characteristic at time t postenrollment in days, for example the time-concentration curve. The entire curve $S(t)$ cannot be known exactly given that the marker is measured at a grid of time-points. A PK model will be used to express $S(t)$ as a function of the measured marker readouts and error terms. One approach to the correlates of protection analysis will estimate the “prevention efficacy curve” $PE(S(t) = s)$ defined as

$$PE(S(t) = s) = [1 - (\text{hazard-mAb}(S(t) = s)) / (\text{hazard-control}(S(t) = s))] \times 100\%$$

where $\text{hazard-mAb}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to either mAb group with $S(t) = s$ and $\text{hazard-control}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to the control group who would have had $S(t) = s$ had s/he been assigned to the same mAb group (thus $S(t)$ is a counterfactual random variable for control recipients). Similar parameters are used for assessing time-dependent correlates of protection in vaccine efficacy trials. A time-dependent parameter is used because interest centers on understanding how the current value of a mAb marker associates with the level of instantaneous PE given exposure with an HIV-1 virus at that time. The statistical analysis plan will describe the methods used to estimate $PE(s)$ over the range of values s of a mAb marker characteristic. In addition to estimation, hypothesis testing will be performed to assess whether a mAb marker modifies PE, ie, testing

$$H_0: PE(S(t) = s) = PE \text{ versus } H_1: PE(S(t) = s) \text{ varies in } s. \quad (1)$$

Rejecting H_0 in favor of H_1 supports the role of the marker in protection. The correlates of protection analysis pools over the two mAb groups, for the purpose of improving power both through a larger sample size and through greater inter-individual variability of the mAb markers. Given that the exact dates of infusions have a major impact on mAb markers $S(t)$ such as concentration over time (eg, notice the profound influence of missed

infusions on $S(t)$ in Figure 2-9, the analysis accounts for the exact dates of infusions that are expected to show considerable heterogeneity across trial participants.

4.13.7.3 A time-window approach to assessing mAb correlates of protection

To explain the concept of this approach, first suppose all participants received all scheduled infusions and rigidly followed the visit schedule. Then this approach compares HIV-1 incidence during the first 4 weeks of the infusion intervals (ie, weeks 1-4, 9-12, 17-20, ..., 73-76) to HIV-1 incidence during the second 4 weeks of the infusion intervals (ie, weeks 5-8, 13-16, 21-24, ..., 77-80), aggregating over the ten 8-week infusion intervals. Because the mAb has much higher concentration during the first halves of the infusion intervals compared to the second halves (eg, demonstrated in Figure 2-9), detection of higher HIV-1 incidence in the second halves of visit windows would imply that higher concentrations are associated with a lower rate of HIV-1 infection.

However, because of missed infusions and the heterogeneity among participants of infusion dates (which is allowable as specified by broad visit windows), a better approach accounts for the set of exact infusion dates of each participant. As such, our approach to implementing the time-window approach compares the mean time between the last infusion and infection for VRC01 group cases, with the mean of the participant-specific weighted average time between infusions of VRC01 group control participants, where the weights allow for changing HIV-1 incidence over time. The analysis stratifies by the 10 mg/kg and 30 mg/kg dose groups and aggregates estimates over these two dose groups. In addition, an important element of the analysis uses predictions of the HIV-1 infection times for all VRC01 group cases. Models for these predictions are built using information on HIV-1 diagnostic tests, intra-host diversity of HIV-1 sequences, HIV-1 viral loads, and perhaps other factors. Initial research to build predictors of HIV-1 infection time based on HIV-1 sequence information has been conducted using validation data sets of acutely HIV-1 infected individuals [127].

A related approach to assessing correlates of protection integrates a pharmacokinetic model of the serum concentration of VRC01 over time, comparing the mean VRC01 concentration at the time of HIV infection for VRC01 group cases with the mean of participant-specific weighted average VRC01 concentrations over follow-up time. The participant-specific average VRC01 concentration over follow-up time is intended to reflect the expected concentration at the time of a random HIV exposure, with weighting used as above to allow for changing HIV-1 incidence over time. Details of these statistical methods will be provided in the statistical analysis plan.

4.13.7.4 mAb markers

For effector function markers measured based on a sample from a mAb recipient, the markers are measured to each of a panel of HIV-1 Envelope proteins. The most relevant HIV-1 Env panel represents the VRC01 antibody footprint diversity of viruses exposing trial participants. For example, relevant for the study population of North/South American MSM + TG, Figure 4-8 shows a logo plot of the VRC01 antibody footprint motifs comprising 35 amino acid sites [128,129] based on 276 subtype B US and South American sequences deposited in the Los Alamos National Laboratory (LANL) sequence database between 2006 and 2014. There are 272 unique mAb footprints.



Figure 4-8 Logo plot of the VRC01 antibody footprints that occur in 276 subtype B US and South American sequences deposited in the LANL sequence database between 2006 and 2014

During the conduct of the trial the research team will determine a minimal set of Envs constituting a panel capturing most of the VRC01 mAb footprint diversity of exposing viruses. One effector function marker of interest for assessing as a correlate of protection is the weighted area under the magnitude-breadth neutralization curve of the mAb footprint Env panel, where the weighting is by the estimated prevalence of mAb footprints in HIV-1s circulating at the trial sites during the trial.

For mAb group participants with a primary study endpoint (breakthrough HIV-1 infection during the first 80 weeks), an important marker is the level at which his/her pre-infection sample at the time of HIV-1 acquisition neutralizes his/her particular breakthrough virus. (This analysis requires modeling the marker at the time of HIV-1 acquisition based on the available grid of marker measurements.) A result where sera from infected participants generally fail to neutralize their founding viruses would support neutralization as a correlate of protection. This analysis is repeated for other effector functions as a way to discriminate which effector functions are or are not correlates of protection, and to rank the effector functions by their contribution to explaining the level of protection.

4.13.7.5 Statistical power for assessing a mAb marker as a correlate of protection

The marker $S(t)$ must vary within mAb recipients over time and/or among mAb recipients in order to detect a correlate of protection, with more variability in one or both components providing greater statistical power to detect a correlate of protection via testing the null hypothesis of equation/panel (1) above. In essence, to detect correlates of protection it is necessary that a large fraction of person-years at risk are in high protection zones and a large fraction of person-years at risk are in low protection zones. (A “high protection zone” is a period of time during which a mAb recipient has high levels of a marker and high levels of efficacy.) Data from VRC 601, VRC 602, and HVTN 104 show wide variability in the mAb concentration over time, and more limited variability among mAb recipients. HVTN 104 will provide more data on these two aspects of marker variability. The limited among-mAb recipient variability motivates the study design that randomly assigns participants to 2 different mAb doses in order to create inter-individual variability.

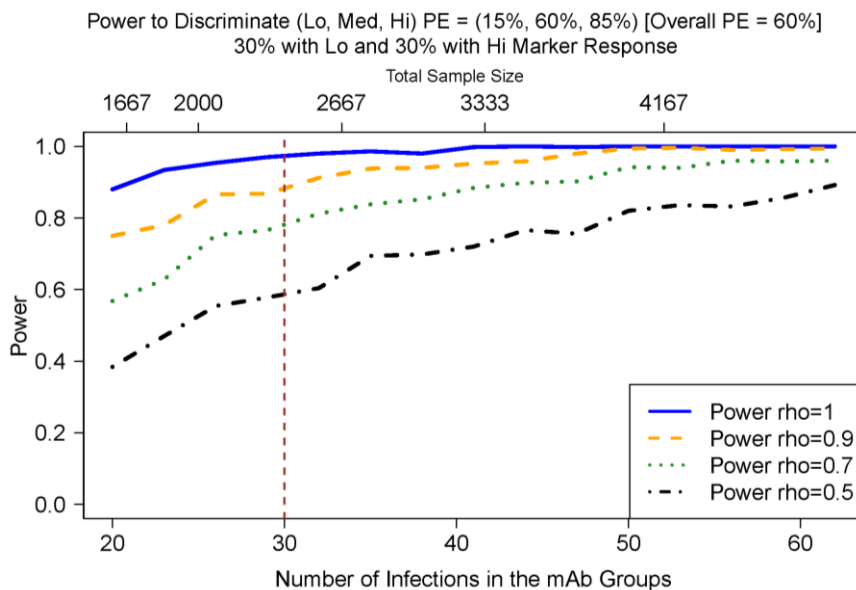
Achieving adequate power to detect correlates of protection requires that the HIV-1 diagnostic testing is more frequent than the infusion schedule. This is why diagnostic visits every 4 weeks are advantageous given infusions every 8 weeks, and procedures may be determined and applied to test for HIV-1 infection more frequently than every 4

weeks. The data from all of the employed diagnostic testing kits is incorporated into the modeling of $S(t)$ and of HIV-1 infection times, and is integrated into the modeling of $S(t)$ and into the statistical analysis for estimation and testing of $PE(S(t) = s)$. Lastly, achieving adequate power to detect correlates of protection requires studying markers that can be measured with a high ratio of potentially protection relevant variability versus protection irrelevant variability, where the latter variability could stem from technical measurement error of the assay or to error in estimation of the timing of infection. Because of this fact the trial design relies on parallel assay studies to qualify marker variables for the analysis and relies on development and characterization of models for $S(t)$ over continuous time t .

We provide one power calculation for assessing a trichotomous marker $S(t)$, the concentration of the mAb at time t post enrolment, as a correlate of protection, which divides the pooled mAb group at a given time t by two thresholds of marker response [$S(t) = 0$ indicates Low, $S(t) = 1$ indicates Medium, and $S(t) = 2$ indicates High for some pre-set definitions of Low, Medium, High]. Thus at any given time t after entry, $S(t)$ divides the pooled mAb group into three subgroups. In our illustration we take “0” to be a VRC01 serum concentration ≤ 50 mcg/mL, “2” to be a VRC01 serum concentration > 10 mcg/mL, and “1” to be an intermediate serum concentration.

Based on Figure 2-4, we conduct a power calculation indexed by the percentage of person-years at-risk of mAb recipients that are in the (Low, Medium, High) zones, and indexed by the level of PE within each of these zones. As indicated in the figure, we expect that about (50%, 40%, and 10%) of the PYRs at risk in the 10 mg/kg mAb group are in the (Low, Medium, and High) regions whereas about (10%, 40%, and 50%) of the PYRs at risk in the 30 mg/kg mAb group are in the (Low, Medium, and High) regions. We consider power calculations pooling data across both mAb groups, assuming 30 mAb HIV-1–infected cases with data and 150 mAb group HIV-1–uninfected controls with data, assuming the design alternatives $PE_{10} = PE_{30} = 60\%$ approximating the numbers displayed in Table 4-3. The detailed mathematical assumptions of these power calculations will be provided in the statistical analysis plan.

Figure 4-9 shows power curves for the scenario that (30%, 40%, 30%) of PYRs at risk are in the (Low, Medium, High) zones (which we approximately expect to occur based on Figure 2-4) and $PE_{10} = PE_{30} = (15\%, 60\%, 85\%)$ in these zones. The power curves also account for noise in the measurement of $S(t)$ via a parameter ρ that equals the proportion of the inter-individual marker variability that is potentially protection relevant. The results show that the noise level majorly affects power, underscoring that only assays meeting qualification criteria will be studied as correlates. The parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values of $S(t)$ are needed. For the scenario that this extra variability reduces ρ to 0.7, there is about 70% power to detect a correlate of protection (with effect size 15%, 60%, 85% efficacy) at the selected trial sample size. Note that the parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values $S(t)$ are needed. A more extensive set of power calculations will be conducted based on HVTN 104 study data.



2-phase logistic regression; 2-sided alpha = 0.05; controls:cases = 5:1

Figure 4-9 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE=15%, 60%, 85%, respectively, for a marker with assay noise parameter $\rho = 1$ (perfect marker), 0.9, 0.7, and 0.5 and percentages of person-years at risk in the (Low, Medium, High) marker regions set at (30%, 40%, 30%). The calculations at 2700 total participants assume 30 mAb group HIV-1–infected cases and 150 mAb group HIV-1–uninfected controls with data on $S(t)$ and pool over both mAb groups. The dashed vertical line represents the sample size of the study.

Figure 4-10 shows the same power analysis as Figure 4-9, fixing $\rho = 0.9$ (indicating a qualifying assay) and varying the percentage of PYRs at risk that are in the (Low, Medium, High) zones. The results show that power increases sharply with the percentage of mAb recipients that are in the Low and High regions, demonstrating the principle that variability in the marker is a strong determinant of power to detect a correlate of protection. For example, the figure shows that the trial has 80% power for the PE = 15%, 60%, 85% effect size if 25%, 50%, 25% of PYRs at risk are in the (Low, Medium, High) zones.

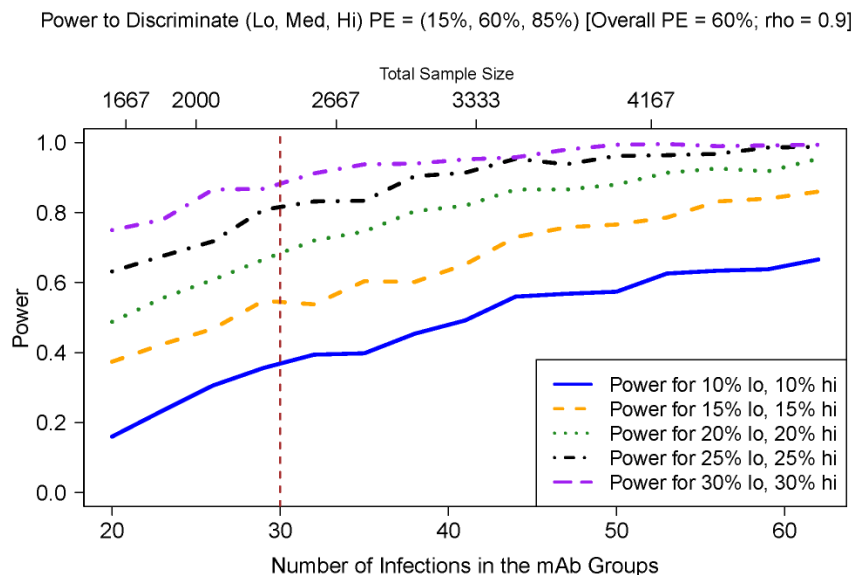


Figure 4-10 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE = 15%, 60%, 85%, respectively, for a marker with assay noise parameter $\rho = 0.9$ and percentages of person-years at risk in the Low and High marker regions varied from 10%, 15%, 20%, 25%, 30%. The calculations at 2700 total participants assume 30 mAb group HIV-1-infected cases and 150 mAb group HIV-1-uninfected controls with data on $S(t)$ and pool over both mAb groups.

4.13.7.6 Genotypic and phenotypic sieve analysis

Genotypic sieve analysis analyzes sequences of breakthrough HIV-1 infecting viruses from the earliest available postinfection sample and seeks to identify amino acid “signatures” that differentiate breakthrough sequences in the mAb groups versus the control group, in terms of differential PE against HIV-1s according to some genotypic characteristics. For example, the genotypic sieve analysis assesses differential PE against different genotypes of HIV-1 with genotype defined by:

- Number of mismatches to the VRC01 mAb footprint of the subtype B consensus sequence (subtype selected to match the circulating HIV-1s)
- Number of known mAb neutralization escape mutations in the mAb footprint
- Number of known mAb effector function escape mutations in the mAb footprint for non-neutralization effector functions such as ADCC, virion capture, and phagocytosis
- Number of potential N-linked glycosylation (PNG) sites within a given radius of the mAb footprint
- Length of variable loops in proximity to the mAb footprint

To illustrate the utility of genotypic sieve analysis, we consider a hypothetical result that would support that the mAb protects via specific neutralization targeting of the mAb’s epitope. In this illustration, the HIV-1 genotype is defined by four ordered genotypes according to whether there are 0, 1, 2, or >2 neutralization escape mutations in the VRC01 mAb antibody footprint. The hypothetical result would be an estimated PE of 95% against HIV-1s with zero escape mutations and a PE of 0% against HIV-1s with >2

neutralization escape mutations, and intermediate and monotone decreasing level of estimated PE against HIV-1 with one mutation and two mutations, respectively.

A second type of sieve analysis, phenotypic sieve analysis, compares breakthrough viruses between the mAb versus control groups using an immunological assay. Specifically, data from an “effector function checkerboard” is filled out, with the rows representing serum samples from a random sample of mAb recipients HIV-1 uninfected at the time of sampling, and the columns representing HIV-1 Env VRC01 footprint targets created from the breakthrough viruses. The phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to mAb recipient sera between the mAb and control treatment groups. A second version of the phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to the VRC01 mAb between the treatment groups; this latter analysis is simpler, based on a single column of data instead of a matrix, because it does not use mAb recipient sera. For an example of the second type of phenotypic sieve analysis, the TZM-bl neutralization assay could be performed on all control breakthrough HIV-1s versus VRC01 and on all mAb group breakthrough HIV-1s (pooled over the two mAb groups) versus VRC01, and a Wilcoxon rank sum test applied to assess a difference. Reduced TZM-bl neutralization sensitivity of the mAb breakthrough group viruses would support that neutralization had a role in protection and that the TZM-bl assay was able to detect this role, and would support using the TZM-bl assay as a tool for evaluating future candidate HIV-1 vaccines. The HVTN has previously conducted neutralization sieve analysis [130]. Figure 4-11 illustrates a genotypic and phenotypic sieve analysis.

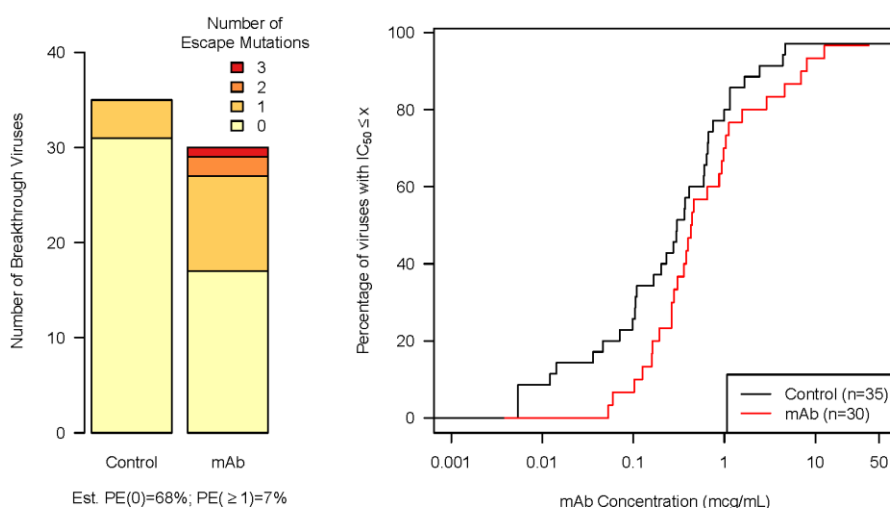


Figure 4-11 Illustration of genotypic (left panel) and phenotypic (right panel) sieve analysis, where the left panel shows the distribution of the number of known neutralization escape mutations in breakthrough control and mAb group HIV-1 sequences, and the right panel shows the percentage of the panel of breakthrough HIV-1s that are neutralized at level 50% (IC₅₀) by the given concentration of the VRC01 mAb.

Another phenotypic sieve analysis focuses on mAb group cases, and measures different effector functions of closest-to-infection participant serum samples or of the VRC01 mAb against the participant-matched breakthrough HIV-1s. The effector functions that tend to have low readouts against participant-matched breakthrough viruses compared to against the panel of control group HIV-1s or compared to an historic panel of HIV-1s are implicated as potential correlates of protection.

In addition, an important sieve analysis will assess PE against HIV-1s that are sensitive to neutralization by VRC01 as measured using the first post-infection sample (sensitive is defined by positive neutralization based on IC_{50} or IC_{80}). This PE parameter measuring prevention efficacy against neutralization sensitive HIV-1s is estimated (with confidence intervals and p-values) in the same way as genotype-specific PE described above. In addition, the same hypothesis testing procedure for detecting differential PE by two HIV-1 genotypes is applied for assessing differential PE by neutralization sensitive versus resistant HIV-1. Moreover, this sieve analysis of sensitive versus resist HIV-1 is also conducted with sensitive/resistant defined by positive/negative response of other assays besides neutralization (eg, ADCC, ADPCP).

4.13.7.7 Illustration of power to detect a phenotypic sieve effect

We conduct power calculations based on TZM-bl neutralization IC_{50} values (in mcg/mL) of VRC07 (a close cousin of VRC01) to approximately 100 viruses representing global HIV-1 diversity (data provided by Mark Louder, Robert Bailer, and John Mascola from the VRC). From the control group we sample 35 HIV-1 infections with IC_{50} from the VRC07 data set, and from the pooled mAb group we sample 30 HIV-1 infections with IC_{50} values bias sampled based on IC_{50} -dependent PE, with $PE(x)$ the probability an infected control recipient would be infected had he (or she) received the mAb with IC_{50} value of x to the exposing virus. Figure 4-12 shows power for comparing the VRC01 IC_{50} distribution of the pooled mAb group HIV-1s versus the control group HIV-1s, based on a two-sample Wilcoxon rank sum test. The effect size indexing a difference between the two groups is equivalently expressed in terms of the $PE(x)$ function (where a horizontal line indicates the null hypothesis of no difference) or in terms of a different cumulative distribution function of the IC_{50} in the two groups. Four correlates effect sizes are considered, ranging from the weakest (Effect Size 1) to the strongest (Effect Size 4). The results show that there is moderate power to detect Effect Size 3 phenotypic sieve effects (second steepest curve in Figure 4-12, power = 0.793).

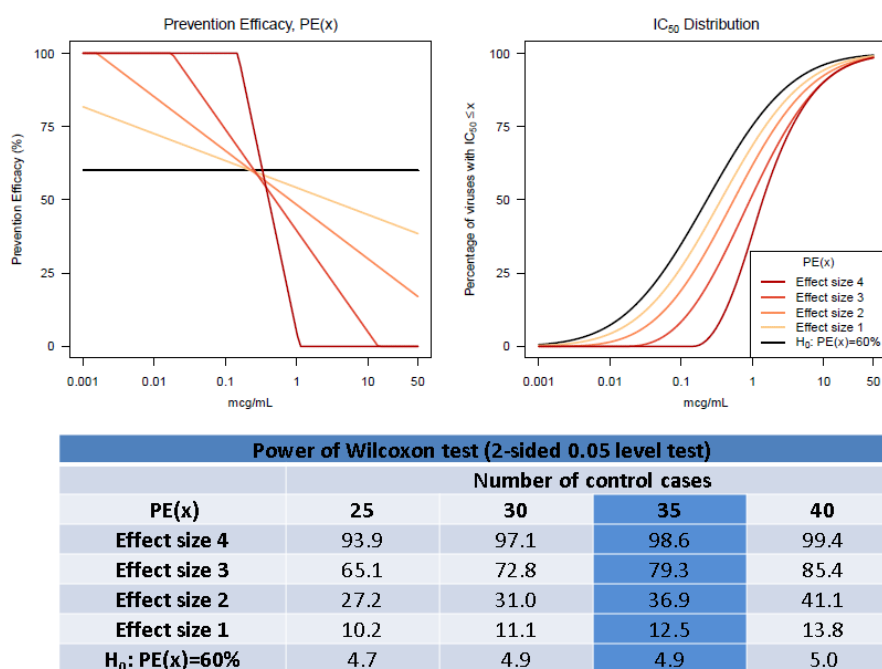


Figure 4-12 Power calculations for comparing IC_{50} distributions between mAb group breakthrough HIV-1s and control group breakthrough HIV-1s, with difference equivalently

expressed in terms of the PE(x) curve or the cumulative IC₅₀ distribution functions, where in the right panel the black/highest curve represents the distribution for the control group breakthrough HIV-1s.

Effect Size 3 is biologically plausible based on the following argument. Under the design alternative of 60% PE we expect a transition between full protection against the most sensitive viruses and zero protection against the most resistant viruses. Table 4-7 shows the percentage of susceptible viruses that are completely blocked by the VRC01 antibody and the percentage of viruses that are completely resistant to the antibody for each of the four specified effect sizes PE(x) in Figure 4-12. For example, for Effect Size 3, the most susceptible 11.6% of viruses are completely blocked (PE = 100%) while the most resistant 2.8% of viruses are completely resistant (PE = 0%) and there is a gradient of protection for the 85.6% of intermediate viruses between the two poles (Table 4-7). The wide range of neutralization (and Fc effector function) sensitivities of HIV-1s suggests that this range of prevention efficacies is plausible. For this effect size there is 79.3% power to detect a phenotypic sieve effect and hence a correlate of protection.

Table 4-7 Percentages of HIV-1s fully susceptible to VRC01 (PE = 100%) and fully resistant to VRC01 (PE = 0%) for the four different effect sizes studied in Figure 4-12

PE(x) Effect Size in Figure 1-16	<i>Susceptible</i> [PE = 100%]	<i>Resistant</i> [PE = 0%]
Effect Size 4	41.9%	23.3%
Effect Size 3	11.6%	2.8%
Effect Size 2	1.0%	<0.1%
Effect Size 1	<0.1%	<0.1%
Null Hypothesis	NA	NA

The sieve analyses will be done including all MITT infected participants, as well as only including mAb group infected participants who received an infusion at the beginning of the 8-weekly interval during which HIV-1 infection was diagnosed.

5 Selection and withdrawal of participants

Participants will be healthy, HIV-uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or serum mAb concentration and efficacy difficult, and some volunteers may be poor candidates for retention.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections 5.1 and 5.2.

5.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 50 years
2. **Access to a participating CRS** and willingness to be followed for the planned duration of the study
3. Ability and willingness to provide **informed consent**
4. **Assessment of understanding:** volunteer demonstrates understanding of this study and completes a questionnaire prior to first infusion with verbal demonstration of understanding of all questionnaire items answered incorrectly
5. **Agrees not to enroll in another study** of an investigational research agent for the duration of the participant's trial participation
6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

7. Willingness to receive **HIV test results**
8. Willingness to **discuss HIV infection risks** and amenable to HIV risk reduction counseling

9. **Persons born Male or identifying as Transgender (TG)** (male-to-female or female-to-male, see HVTN 704/HPTN 085 SSP) who, in the 6 months prior to randomization, experienced 1 or both of the following HIV risk criteria:

- Condomless anal intercourse with 1 or more male or transgender partner(s)
- Anal intercourse with 2 or more male or transgender partners

Note: Receipt of hormonal therapy does not make a TG volunteer ineligible.

Volunteers who have been in a mutually monogamous relationship with an HIV-1 seronegative partner for > 1 year are excluded.

Laboratory Inclusion Values

Hematology

10. **Hemoglobin** (Hgb) ≥ 10.5 g/dL for volunteers who were born female, ≥ 13.0 g/dL for volunteers who were born male (≥ 12.0 g/dL for transgender women taking feminizing hormones [eg, anti-androgens, estrogens])
11. **Platelets** $\geq 100,000$ cells/mm³

Chemistry

12. **ALT** < 2.5 times the institutional upper limit of normal and creatinine ≤ 1.25 times the institutional upper limit of normal

Virology

13. **HIV uninfected, as defined in the SSP, within 30 days prior to enrollment**

Urine

14. **Negative, trace, or 1+ (30 g/L for semi-quantitative) urine protein by dipstick**

Reproductive Status

15. **Volunteers capable of becoming pregnant:** negative serum or urine beta human chorionic gonadotropin (β -HCG) pregnancy test performed at the screening visit and prior to infusion on the day of initial infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.
16. **Reproductive status:** A volunteer who is capable of becoming pregnant must agree to consistently use effective contraception (see Appendix B, and SSP) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit.
17. **Volunteers capable of becoming pregnant must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

5.2 Exclusion criteria

General

1. **Investigational research agents** received within 30 days before first infusion
2. **Body mass index (BMI) ≥ 40**
3. **Pregnant or breastfeeding**
4. **Any reactive, indeterminate, or positive HIV test**, even if subsequent testing indicates that the individual is not HIV infected, except as permitted by the HVTN 704/HPTN 085 PSRT.

Vaccines

5. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 704/HPTN 085 PSRT will determine eligibility on a case-by-case basis.

Immune System

6. **Serious adverse reactions to VRC01 formulation components such as sodium citrate, sodium chloride, and L-arginine hydrochloride**, including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.
7. **Autoimmune disease**, including Type I diabetes mellitus (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require consistent immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate reactogenicity and AE assessments)
8. **Immunodeficiency syndrome**

Clinically significant medical conditions

9. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:
 - Any contraindication to repeated infusions or blood draws, including inability to establish venous access;
 - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period; or
 - A condition or process for which signs or symptoms could be confused with reactions to VRC01.
10. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence,

assessment of safety or infusion reactions, or a volunteer's ability to give informed consent

11. **Psychiatric condition that precludes compliance with the protocol.** Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
12. **Asthma**, other than mild, well-controlled asthma
13. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
14. **Malignancy** (Not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study)
15. **Seizure disorder:** History of seizure(s) within past three years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.
16. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema
17. History of **receiving transplantation of life-saving organs or tissues** (includes heart, kidney, pancreas, lungs, liver, and intestines)
18. **Known hepatic or renal dysfunction**

5.3 Participant departure from infusion schedule or withdrawal

This section concerns an individual participant's departure from the infusion schedule. Pause rules for the trial as a whole are described in Section 10.3.

5.3.1 Delaying infusions for a participant

Under certain circumstances, a participant's scheduled infusion will be delayed. The factors to be considered in such a decision include but are not limited to the following:

- Prior to infusion, abnormal vital signs or clinical symptoms that may mask assessment of a study product reaction
- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delay or withdrawal from the infusion schedule. The investigator may consult with the HVTN 704/HPTN 085 PSRT.
- Pregnancy: for participants who become pregnant infusions will be stopped. If the participant is no longer pregnant (as demonstrated by a negative urine or serum pregnancy test) and wants to continue with infusions, the HVTN 704/HPTN 085 PSRT will be consulted to determine whether the participant may resume infusions or whether infusions should be permanently discontinued.

5.3.2 Participant departure from infusion schedule

Every effort should be made to follow the infusion schedule per the protocol. If a participant misses an infusion and the visit window period for the infusion has passed, then sites may consult the SSP.

5.3.3 Discontinuing infusions for a participant

Under certain circumstances, an individual participant's infusions will be permanently discontinued. Specific events that will result in stopping a participant's infusion schedule include:

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of infusions may be granted with the unanimous consent of the HVTN 704/HPTN 085 PSRT);
- Clinically significant condition (ie, a condition that affects the immune system or for which continued infusions and/or blood draws may pose additional risk), including but not limited to the following:
 - Any grade 4 local or systemic reactogenicity symptom or AE that is subsequently considered to be related to study product;
 - An SAE that is subsequently considered to be related to study product;
 - Any grade 3 clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to study product;
 - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product;
 - Clinically significant hypersensitivity reaction including but not limited to type 1 hypersensitivity reaction and/or serum sickness associated with study product. Consultation with the HVTN 704/HPTN 085 PSRT is required prior to subsequent infusion following any hypersensitivity reaction associated with study product; or
- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).

Infusions will be permanently discontinued for a participant diagnosed with HIV infection or with 2 reactive HIV tests, even if subsequent testing indicates that the participant is not HIV infected.

Participants for whom infusions are discontinued for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in Schedule 4 follow-up visits and protocol-specified procedures (see Appendix I and Appendix M), unless medically contraindicated.

5.3.4 Participant termination from the study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation

- Participant relocates and remote follow-up or transfer to another CRS is not possible
- CRS determines that the participant is lost to follow-up
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff)
- Any condition where termination from the study is required by applicable regulations.

6 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 1-1. See the IBs for further information about study products.

6.1 Study product regimen

The schedule of study product administrations is shown in Section 1 and additional information is given below.

Group 1

Treatment 1 (T1): VRC-HIVMAB060-00-AB 10 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to prepare a final total volume of 150 mL to be administered IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 2

Treatment 2 (T2): VRC-HIVMAB060-00-AB 30 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to prepare a final total volume of 150 mL to be administered IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 3

Control 3 (C3): Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) to be prepared as a final total volume of 150 mL to be administered IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

6.2 Study product formulation

VRC-HIVMAB060-00-AB [VRC01, Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB]

VRC01 will be provided as a sterile clear, colorless to yellow isotonic solution, essentially free of visible particles; some opaque or translucent particles may be present. Each vial contains 100 mg / mL of VRC-HIVMAB060-00-AB in formulation buffer. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and do NOT contain a preservative. The product should be stored frozen -35°C to -15°C with excursions permitted between -45°C and -10°C. The study products are described in further detail in the IB.

Prior to preparation, vials containing VRC01 must be removed from the freezer and thawed for a minimum of 1 hour at room temperature. Following this 1 hour thaw, the unopened vials of VRC01 may be stored for up to 24 hours at room temperature (not to exceed 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may NOT be thawed or stored in direct sunlight. Once thawed, product may NOT be refrozen.

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. These particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation has no effect on product quality. If the particles do not disappear at room temperature, the vials should be placed in the refrigerator, as particles may continue to dissipate at 2°C to 8°C (36°F to 46°F). Vials that continue to have visible particles after a maximum of 24 hours at controlled room temperature and/or after 4 weeks at 2°C to 8°C (36°F to 46°F) should not be used. Instead, those vials with particles still visible should be quarantined [at 2°C to 8°C (36°F to 46°F)] until they are returned to the NIAID Clinical Research Products Management Center (CRPMC) (or manufacturer upon request of the CRPMC) or destroyed if directed by the CRPMC.

Control for VRC01 [Sodium Chloride for Injection USP, 0.9%]

Sodium Chloride for Injection USP, 0.9% will be used as the Control for VRC01. It must be stored as directed by the manufacturer. For sites who do not have access to Sodium Chloride for Injection USP, 0.9%, the Sodium Chloride for Injection, 0.9% that they use must meet the following criteria: a sterile solution of Sodium Chloride in Water for Injection which contains no antimicrobial agents. It is nonpyrogenic and is intended for intravenous administration.

6.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription **MUST** contain the participant's weight based upon the participant's weight at the most recent visit where weight was measured (this includes screening) and randomization code (this may NOT be communicated verbally). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 38 General Chapter Physical Tests / <797> Pharmaceutical Compounding - Sterile, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

6.3.1 VRC-HIVMAB060-00-AB (10mg/kg IV) - (Group 1)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($10 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for up to 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.2 VRC-HIVMAB060-00-AB (30mg/kg IV) - (Group 2)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($30 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will then add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.3 Control for VRC01 (Group 3)

To prepare an IV infusion, the pharmacist, using aseptic technique, will add 50 mL of Sodium Chloride for Injection USP, 0.9% to a 100 mL bag of Sodium Chloride for Injection USP, 0.9%. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

6.4 Administration

VRC01 or Control (Intravenously)

Prior to infusion, if the VRC01 or Control IV bag has been stored at 2°C to 8°C, the bag must be equilibrated to room temperature (maximum of 30°C) for 30 minutes or longer and may be held for up to 8 hours, including equilibration time and completion of product administration. (NOTE: This 8 hour period may NOT exceed the DO NOT INFUSE after date and time on the IV bag label.)

The IV bag prepared by the pharmacy will include the weight that was used for preparation of the IV bag (VRC01 or Control). The clinician responsible for administration will check the bag label and confirm that the participant identifier is correct and that the weight on the bag label is within 10% of the participant’s current actual weight (refer to Section 6.3 for more information).

An in-line filter infusion set must be used for IV administration (see SSP for specifications and additional details).

The entire contents of the investigational study product solution will typically be administered IV over about 15 to 60 minutes using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as participant tolerance.

6.5 Acquisition of study products

VRC-HIVMAB060-00-AB is provided by the VRC/DAIDS/NIAID.

Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) will not be provided through the protocol and must be obtained by the site.

Once a CRS is protocol registered, the pharmacist can obtain study products from the CRPMC by following the ordering procedures given in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

6.6 Pharmacy records

The CRS pharmacist is required to maintain complete records of all study products. The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

6.7 Final disposition of study products

All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the CRPMC. The procedures and relevant form are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

7 Clinical procedures

The schedules of clinical procedures are shown in Appendix J through Appendix M.

7.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The informed consent form documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in this study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the participant and the review should be documented. At each study visit, CRS staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information is learned that might affect the participants' decisions to stay in the trial, this information will be shared with trial participants. If necessary, participants will be asked to sign revised informed consent forms.

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to their Institutional Review Board/Ethics Committee (IRB/EC) and any applicable Regulatory Entity (RE) for human subjects protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is “Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs [informed consent forms] prior to implementation at a site.” CRSs are responsible for knowing the requirements of their applicable REs.

7.1.1 Screening consent form

Without a general screening consent, screening for a specific study cannot take place until the site receives protocol registration from the DAIDS RSC Protocol Registration Office.

Some CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV prevention trial. In this way, CRS staff can continually screen potential participants and, when needed, proceed quickly to obtain protocol-specific enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time period specified in the eligibility criteria.

7.1.2 Protocol-specific consent forms

The protocol-specific consent forms describe the study products to be used and all aspects of protocol participation, including screening and enrollment procedures. A sample protocol-specific consent form for the main study is located in Appendix A. A separate sample consent form for other uses of specimens is located in Appendix C.

Each CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in Appendix A and Appendix C. The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC, and any applicable RE
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their site-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the level of understandability.

The sample informed consent form includes instructions throughout the document for developing specific content.

Sites should follow the instructions in the Protocol-specific Official Memo distributed along with this protocol regarding when they may begin using their site-specific protocol consent forms.

Regarding protocol registration, sites should follow procedures outlined in the current version of the DAIDS Protocol Registration Manual.

7.1.3 Assessment of Understanding

Study staff are responsible for ensuring that participants fully understand the study before enrolling them. This process involves reviewing the informed consent form with the participant, allowing time for the participant to reflect on the procedures and issues presented, and answering all questions completely.

An Assessment of Understanding is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary. Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

IRB/EC and any applicable RE may require that a participant has signed either a screening or protocol-specific consent document prior to administering the Assessment of Understanding. The consent process (including the use of the Assessment of Understanding) should be explained thoroughly to the IRB/EC and any applicable RE, whose recommendations should be followed.

7.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before infusion on Day 0. All inclusion and exclusion criteria must be assessed within 56 days before enrollment, with the exception of HIV testing, which must be performed within 30 days before enrollment (see Section 5.1), unless otherwise specified in the eligibility criteria (or below in this section).

After the appropriate informed consent has been obtained and before enrollment, the following procedures are performed:

- Medical history, documented in the case history record;
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots;
- Laboratory tests as defined in the inclusion and exclusion criteria, including:
 - Screening HIV testing at local lab (see SSP)
 - CBC with differential
 - ALT
 - Creatinine
 - Urine dipstick
 - Urine or serum pregnancy test (volunteers capable of becoming pregnant); Persons who are not capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Assessment of participant risk for HIV infection
- Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>);
- Counseling on HIV testing and risk reduction, performed in compliance with US CDC current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 7.5; and
- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in the study inclusion criteria and in Appendix B. Discussion of pregnancy prevention includes advising a participant who is capable of becoming pregnant but who reports no current sexual activity that could lead to pregnancy to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

7.2.1 Use of screening results from another HVTN or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this study, and the tests were conducted within the time periods specified in the eligibility criteria (see Section 5).

7.3 Enrollment and infusion visits

Enrollment is simultaneous with first infusion. The time interval between randomization and enrollment should not exceed 4 working days. The CRS requests the randomization assignment from the Web-based randomization system. Circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all infusion visits, the following procedures are performed before infusion:

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- Assessment of baseline reactogenicity parameters;
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- Assessment of concomitant medications (as described in Section 7.2);
- ALT;
- Creatinine;
- CBC with differential;
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Blood collection for HIV testing, PrEP monitoring, and sample storage.

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (see Sections 6.3 and 6.4).

Administration of an infusion and infusion-related procedures must be accomplished within 1 calendar day.

Immediately following the first infusion, the participant remains in the clinic for observation and initial reactogenicity assessment. See the SSP for details regarding infusion visit protocols and subsequent infusion observation and reactogenicity assessment procedures that CRSs must follow. The site will make arrangements to obtain a report of reactogenicity events from the participant after the 3-day reactogenicity period (as described in Section 7.10 and in the SSP).

The following procedures will be performed at all infusion visits. These procedures may be performed prior to, during, or following infusion:

- Administration of the participant questionnaire which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling);
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Risk reduction counseling (as described in Section 7.5);
- For participants capable of becoming pregnant, pregnancy prevention assessment (as described in Section 7.2 and 7.6);
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled visits as specified in Appendix J:

- Syphilis serology testing;
- Gonorrhea (GC)/chlamydia (CT) testing by urine and rectal swabs, and GC testing by oropharyngeal swab; and
- Urine dipstick (see Section 7.9).

7.4 Post-infusion visits for HIV-uninfected study participants

The following procedures are performed at all post-infusion follow-up visits for HIV-uninfected study participants:

- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Blood collection for HIV testing, PrEP monitoring, and sample storage; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled follow-up visits as specified in Appendix F and Appendix J:

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Administration of participant questionnaire, which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling)
- Risk reduction counseling (as described in Section 7.5);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- For participants who are capable of becoming pregnant, pregnancy prevention assessment (as described in Section 7.2 and 7.8);
- Assessment of new or unresolved AEs/intercurrent illnesses;
- Urine dipstick (see Section 7.9); and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.5 HIV counseling and testing

HIV counseling will be performed in compliance with the CDC's guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the protocol-specific HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection. In addition, study participants will be provided with HIV prevention supplies and referral to providers of PrEP per local and regional guidelines. Study investigators will ensure that participants have access to standards of care for HIV prevention in their local settings. As new data emerge and standards of care for HIV prevention evolve, both the content of risk reduction counseling and referrals for biomedical interventions will be updated to conform to current best practices for the populations enrolled in this trial. For additional details regarding PrEP provision and referrals, see the HVTN 704/HPTN 085 website.

7.5.1 Study product–related seroreactivity

Human sera containing purified VRC01 at concentrations up to 1600 mcg/mL have been tested using a variety of commercially available HIV test kits without any indication of reactivity. For this reason, we do not anticipate that receipt of VRC01 will cause a reactive result on currently available HIV test kits, but this remains a theoretical possibility.

Because this possibility cannot be categorically eliminated, study staff will advise study participants to confine their HIV testing while in the study to that provided through the CRS. Staff will also inform study participants of the likelihood of routine HIV testing

being offered or performed outside the study CRS at emergency rooms, clinics, and medical offices and will inform participants of their right to opt out of HIV testing outside the study site. CRS staff should inform study participants if local and/or state/regional policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline HIV testing preemptively. CRS staff should also inform participants if positive HIV test results must be reported to local public health authorities. CRS staff should also inform participants of the need to maintain study blinding by getting HIV testing only at the study CRS. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV mAb clinical trial and should only be tested for HIV at the study CRS.

Study staff should also stress that the study product is completely cleared from the body within a few months, so even the theoretical risk of VRC01 causing a misleading HIV test result will disappear before their final scheduled clinic visit.

7.6 Follow-up visits for HIV-infected participants

The following procedures are performed at scheduled follow-up visits as specified in Appendix G, Appendix H, Appendix K, and Appendix L:

- Counseling on HIV testing and diagnosis;
- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- ART assessment;
- Assessment of concomitant medications (as described in Section 7.2);
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV transmission risk reduction counseling;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, viral load testing, VRC01 Ab levels, functional assays, viral isolation/sequencing, and sample storage (see Appendix G, Appendix H, and Section 8.5);
- Blood collection for CD4+ T cell counts;
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and

- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.7 Follow-up visits for participants who discontinue infusions for reasons other than HIV infection

Participants for whom infusions are discontinued for reasons other than HIV infection should be encouraged to continue in the study. For such participants, the following procedures are performed at approximately quarterly scheduled follow-up visits as specified in Appendix I and Appendix M:

- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- Risk reduction counseling (as described in Section 7.5);
- Assessment of concomitant medications (as described in Section 7.2);
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, PrEP monitoring, CBC/differential, ALT, creatinine, VRC01 Ab levels, functional assays, and sample storage (see Appendix I and Appendix M);
- Urine dipstick (see Section 7.9);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.8 Contraception status

Contraception status is assessed and documented at screening and infusion visits for a participant who is capable of becoming pregnant. Prior to enrollment and throughout the

study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. These participants should be reminded regularly of the importance of using contraception and should be referred to specific counseling, information, and advice as needed. (See Appendix B for further detail.) This reminder should be documented in the participant's study record.

Infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation—must be documented in the participant's study record.

7.9 Urine testing

Urine dipstick testing may be performed in the clinic or the lab. The following analytes should be analyzed and recorded: specific gravity, protein, blood/hemoglobin, pH, urobilinogen, bilirubin, ketone, leucocyte esterase, nitrite, and glucose. The examination is performed on urine obtained by clean catch. Urine microscopy is required when the protein result is 1+, 2+, 3+, or 4+ (or semi-quantitative 30, 100, 300, or 2000 g/L) and/or the blood/hemoglobin result is trace, 1+, 2+, 3+, or 4+, but not required (unless otherwise clinically indicated) if the dipstick result is abnormal due to non-urinary bleeding.

If the dipstick performed for screening is transiently abnormal with an exclusionary result (eg, 2+ proteinuria), then repeat the dipstick and, if within the eligibility limits specified in the protocol, the participant may be enrolled (see SSP for further detail).

A follow-up urine test should be deferred if a participant is experiencing non-urinary bleeding (eg, menstruation), but should be performed as soon as possible. If a follow-up dipstick is abnormal due to non-urinary bleeding (eg, a participant's menstrual period), document in the comment section of the CRF and repeat the dipstick once the participant is no longer experiencing non-urinary bleeding. In this case, a urine microscopy is not required (see SSP for further detail). If a follow-up dipstick is abnormal due to infection, document this issue in the participant's source documentation and provide appropriate treatment and/or referral.

7.10 Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after infusions per the SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.1, dated March 2017, except as noted in Section 10.2.2.

The reactogenicity assessment period is 3 full days following each infusion. The site staff and the participant will be in contact after the 3-day reactogenicity period, or sooner if indicated. At that time, site staff will discuss reactogenicity events with the participant and record the relevant information on CRF(s) or participant chart note as source (for more details, see the SSP). Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. Participants are instructed to contact the clinic for events that arise during the period between infusion and the next scheduled visit. In

general, a participant who self-reports any postinfusion reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity events are reported using CRFs that correspond to the time of assessment per the SSP. Reactogenicity assessments include assessments of specific systemic and local signs and symptoms and infusion site reactions. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of infusion and 3 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse event log form.

7.10.1 Assessment of systemic and local signs and symptoms

Systemic signs and symptoms include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, and vomiting. Local symptoms include pain and/or tenderness proximal to the infusion site. The maximum severity reached for each symptom during the assessment period per the SSP is reported.

7.10.2 Assessment of infusion site

Infusion site reactions may include redness/erythema and induration/swelling. The maximum horizontal and maximum vertical measurements for infusion site redness/erythema and induration/swelling are recorded.

All infusion site reactions are monitored until resolution. Areas greater than 25 cm² are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

7.11 Visit windows and missed visits

Visit windows are defined in the SSP. For a visit not performed within the window period, a Missed Visit form is completed.

If a participant misses a scheduled visit, CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. See the HVTN 704/HPTN 085 SSP for more details. If a participant missed an infusion visit or if infusions must be permanently discontinued, see Section 5.3.2 and Section 5.3.3 for resolution.

7.12 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, ALT, and Creatinine), pregnancy testing, social impact assessment, and HIV test.

7.13 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given during the pregnancy, but remaining visits and study procedures should be completed unless medically contraindicated. For participants who are no longer pregnant, see Section 5.3.1. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome.

8 HIV infection assessment and clinical response

8.1 HIV symptom assessment

At all scheduled visits and at unscheduled visits due to illness or suspected exposure, if necessary, information will be collected about any signs or symptoms suggestive of acute HIV infection. Participants will be counseled about signs and symptoms of acute HIV infection and at visits following recent high-risk exposure, participants will be queried about any signs/symptoms suggestive of acute HIV infection. Presence of signs/symptoms suggestive of acute HIV infection, an intercurrent illness consistent with acute retroviral syndrome, or history of high-risk exposure would prompt a diagnostic work-up per the protocol-specific algorithm for recent exposure to determine HIV infection.

8.2 HIV screening test (prior to randomization)

Prior to randomization, participants will be screened for HIV-1/2 infection by FDA-approved blood tests (non-US sites may use locally available assays that have been approved by HVTN and HPTN Laboratory Operations [see SSP]). Volunteers identified as being HIV infected during screening will be referred for medical treatment and management of the HIV infection. These individuals may also be referred to appropriate ongoing clinical trials or observational studies. For volunteers who have one or more reactive/positive HIV tests, but whose HIV status is inconclusive, any further testing will be performed locally.

8.3 HIV testing postinfusion

Following enrollment, HIV testing will take place at scheduled clinic visits (Appendix F).

HIV testing will be performed using the protocol-specific HIV testing algorithms (see SSP). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV 1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV 1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit (ie, visit #.X specified in Appendix G and Appendix H). Samples to be stored for future studies will also be collected at this time (see Appendix G).

A 'case' will be defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s) (Section 8.4).

The HVTN Laboratory Program is responsible for all in-study diagnostic testing.

8.4 Endpoint adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess.

Therefore, this study will have an endpoint adjudication process to review all serological and virological test results in a blinded manner for each participant who tests positive per the HVTN 704/HPTN 085 HIV diagnostic testing algorithms. Adjudicators will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (ie, HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the VRC and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

8.5 HIV infection during the study

It is critical to the success of the study that HIV-infected participants be properly identified and all data postdiagnosis be carefully recorded. Information obtained from these cases of HIV-1 infection will form the basis of the primary endpoint assessment.

Participants who develop HIV infection following the initial infusion of study product may remain in the study for follow-up but will receive no further infusions. This includes participants for whom infusions were discontinued for reasons other than HIV infection but for whom HIV-1 infection has subsequently been confirmed. All participants who become HIV-1-infected following enrollment through their final study visit will be monitored as indicated in Appendix G and Appendix K.

If a participant is confirmed to have become HIV infected after enrollment, plasma HIV-1 RNA will be measured on archived samples prior to the first positive screening test. HIV-1 RNA testing will also be performed at 2-week intervals up to 8 weeks postdiagnosis, then at 12 and 24 weeks postdiagnosis. In addition to plasma HIV-1 RNA testing, participants will also have specimens drawn for measurements of VRC01 Ab serum levels, neutralization and other antibody functions, viral isolation and sequencing; physical exams, recording of AEs, counseling to reduce HIV transmission risk, and social impact assessments will also be performed at most of these visits.

Longer-term follow-up for these participants may be accomplished through enrollment in another protocol. Archived samples from earlier visits may also be tested to determine the earliest date of HIV infection.

If enrollment visit HIV testing indicates that a participant was HIV infected at enrollment (ie, prior to the first infusion of study product) or a participant is diagnosed with HIV-2 infection following enrollment, then the procedures indicated in the preceding paragraph do not apply. Such participants should be followed as indicated in Appendix H and Appendix L. This also applies to participants for whom infusions are discontinued for reasons other than HIV infection and who subsequently are diagnosed with HIV-2 infection.

8.6 Medical care for participants who become HIV infected

It is anticipated that some study participants, whether they are randomized to receive VRC01 or control, will become HIV infected during the course of the trial. It is critical that these HIV-infected participants receive appropriate medical care.

The investigators associated with this trial will refer participants who develop HIV infection while participating in this trial to medical professionals for care.

9 Laboratory

9.1 CRS laboratory procedures

The SSP provides further guidelines for operational issues concerning the clinical and processing laboratories. This document includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix F through Appendix I. For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, laboratory special instructions will be posted on the protocol-specific section of the HVTN website.

9.2 Total blood volume

Required blood volumes per visit are shown in Appendix F through Appendix H. Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

9.3 Assay timepoints

Endpoint assays are performed on participants at the timepoints shown in Appendix F through Appendix I may be performed at baseline. Assays for humoral and cellular responses may be performed on participants or a subset of participants at other timepoints; the schedules are shown in Appendix F through Appendix I.

9.4 VRC01 mAb levels

VRC01 levels will be measured in serum. An ELISA will be used to determine the concentration of the VRC01 antibody in the serum. The ELISA employs the VRC01 Fab-specific 5C9 mAb, which is an anti-idiotypic antibody cloned from a single B cell that was sorted by flow cytometry using a VRC01 scFv probe. The 4-parameter logistic curve regression of a standard curve of VRC01 covering the range from 0.031 to 1.0 mcg/mL is utilized in this assay to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay. This assay has been qualified but not formally validated. The functional sensitivity for the generation of the ELISA assay format, which is currently used at NVITAL, is 2 mcg/mL and as the technology for this assay continues to develop, an updated assay may be utilized.

9.5 Endpoint assays: humoral

9.5.1 Anti-VRC01 antibody assay

Assessment for development of anti-VRC01 antibodies in participants will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. The assay uses biotin-labeled VRC01 immobilized on a streptavidin-coated MSD plate as the capture molecule, and the SULFO-TAG labeled VRC01 as the reporter molecule. This assay is independent of the anti-VRC01 antibody isotype, and permits the detection of both high and low affinity antibodies.

9.5.2 Neutralizing antibody assay

Depending upon the VRC01 concentrations measured in collected specimens, their capacity to neutralize HIV in blood and mucosal secretions may be evaluated by an in vitro cell-based virus neutralization assay [131-133] using pseudotyped viruses. All specimens testing positive for anti-VRC01 antibodies will be tested for HIV-1 neutralizing activity.

One or more viruses that are among the most sensitive to VRC01 (eg, MN.3 and MW965.26) will be assayed. The IC_{50} of VRC01 against both of these viruses is 0.01 – 0.03 mcg/ml and the TZM-bl assay is validated for this level of sensitivity.

9.6 ARV detection

A direct, biomedical measure is used to assess ARV use in this study. This approach is used because self-report of ARV use for PrEP or PEP and other purposes has been shown to be unreliable in a variety of settings [134-136]. For this study, ARV testing will be performed using a test that measures the amount of tenofovir-diphosphate (a metabolite of tenofovir) in red blood cells. This test utilizes a dried blood spot as the sample source and analyzes for tenofovir diphosphate by liquid chromatography and tandem mass-spectroscopy, as previously described [137,138]. Because of a long half-life, high amounts of the metabolite in the dried blood spot correspond with consistent dosing of Truvada and low amounts correspond with inconsistent dosing [76].

Dried blood spot samples are collected from all participants at all scheduled study visits. Periodically, a subset of participant samples will be tested in a manner that will provide an estimate of PrEP use across clinical sites. Storage of dried blood spots as well as serum and plasma (see Appendix F and Appendix I) will allow additional assessment of PrEP use if warranted. Individual test results will not be returned to study sites or study participants.

9.7 Host (human) genotyping

Various markers, such as genes associated with host immune functions or HIV disease progression may also be assessed.

9.8 Lab assay algorithm

The HVTN Lab Assay Algorithm lists assays that characterize various types of immunologic activity as well as host genetics that may be conducted to characterize the drug activity in this study. Various types of assays may be employed to assess maintenance of functional drug activity at multiple timepoints selected based on drug level outcomes. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

9.9 Possible additional studies

Samples may be used for other testing and research related to furthering the understanding of HIV immunology, monoclonal antibodies, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

9.10 Other use of stored specimens

The Networks store specimens from all study participants indefinitely, unless a participant requests that specimens be destroyed or if required by IRB/EC or RE.

Other use of specimens is defined as studies not described in the protocol.

This research may relate to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases. This could include limited genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other testing on specimens will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs if required.

The protocol sample informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study site investigator or designee must notify HVTN Regulatory Affairs in writing. In either case, HVTN Regulatory Affairs directs the HVTN Lab Program not to use samples from these participants for such other uses.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on other use of specimens.

9.11 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and shipping and handling of all

specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

10 Safety monitoring and safety review

10.1 Safety monitoring and oversight

10.1.1 HVTN 704/HPTN 085 PSRT

The HVTN 704/HPTN 085 PSRT is composed of the following members:

- DAIDS medical officer representatives,
- Protocol chairs and cochairs,
- Protocol Team leader,
- Core medical monitor,
- Clinical safety specialist (CSS), and
- Regional medical liaison (RML).

A medical officer from an organization(s) designated by the study sponsor will also participate in the PSRT.

The clinician members of HVTN 704/HPTN 085 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinators, project managers, study product developer representatives, clinical research manager, clinical trial manager, and others may also be included in HVTN 704/HPTN 085 PSRT meetings.

10.1.2 NIAID DSMB

The NIAID DSMB assesses the effects of the study product during the trial, provides other monitoring as described in Section 4.9.1.1, and may give advice to the HVTN 704/HPTN 085 OC.

10.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 704/HPTN 085 PSRT and NIAID DSMB.

The roles and responsibilities of the HVTN CSS or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 704/HPTN 085 PSRT AE review criteria (see Section 10.3);
- Notifying CRSs and other groups when safety pauses are instituted and lifted (see Section 10.3);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 704/HPTN 085 PSRT.

10.2 Safety reporting

10.2.1 Submission of safety forms to SDMC

Sites must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, concomitant medications) before the end of the next business day after receiving the information. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information.

10.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation subject administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). The AE reporting period for this study comprises the entire study period for each individual participant (from study enrollment until study completion or discontinuation of the study). All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1, dated March 2017, available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>, except that the AEs below will be reported according to the SSP:

- Unintentional weight loss
- Infusion Site Erythema or Redness and Infusion Site Induration or Swelling
- Infusion reactions

In addition, clarifying footnote 16 (page 21) in Version 2.1 of the AE Grading Table, for transgender participants ≥ 13 years of age who have been on feminizing hormone therapy for more than 6 consecutive months, grade hemoglobin based on the female sex at birth hemoglobin lab values. For transgender participants ≥ 13 years of age who have been on masculinizing hormone therapy for more than 6 consecutive months, grade hemoglobin based on the male sex at birth hemoglobin lab values.

As detailed in the SSP, two additional parameters, cytokine release syndrome and serum sickness, have been added to the DAIDS AE Grading Table for HVTN 704/HPTN 085.

AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (Section 10.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 10.2.4).

Sites are expected to notify the CSS or RML of any serious safety concern requiring their attention (see Table 10-1). Telephone numbers and email addresses are found on the HVTN704/HPTN 085 protocol-specific website. Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, the CSS or RML will reply during working hours (ie, US Pacific Time, Peru Time, or South African Standard Time) to confirm that the email has been received and reviewed. If email service is not available, the CRS should notify the CSS or RML of the event by telephone, then submit CRFs.

In addition, site investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

10.2.3 Expedited reporting of adverse events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE Manual), which is available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting>.

For questions about DAERS, please contact NIAID CRMS Support at CRMSsupport@niaid.nih.gov or from within the DAERS application itself.

For questions about expedited AE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

Under ICH E2A (*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*), an SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe),

- requires patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is a medically important event or reaction.

Medical and scientific judgment should be exercised when deciding if other situations are serious. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions not resulting in hospitalization, or development of drug dependency or drug abuse.

The expedited reporting period for this study comprises the entire study period for each individual participant (from study enrolment until study completion or discontinuation from the study).

The study products for which expedited reporting are required are:

- VRC01, and
- Control.

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

If the PSRT believes unblinding of the site PI to treatment assignment will assist with the clinical management of the SAE, the PSRT may consult the independent NIAID DSMB for a recommendation. In the event the PSRT and/or the NIAID DSMB determines that unblinding is indicated, the unblinded statistician, DSMB Chair, or designee will inform the site physician of the participant's treatment assignment in such a manner as to maintain the study blind of the PSRT and study team. For additional impact and management of SAEs on the study, refer to Section 10.3.

10.2.4 Expedited reporting of AEs to pertinent national regulatory authorities

The study sponsor or designee(s) prepares and files expedited reports to appropriate regulatory authorities within the timelines required by pertinent national regulatory authorities.

Site IoRs/designees will submit AE information and any other relevant safety information to their ECs/IRBs in accordance with EC/IRB requirements.

10.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and infusion with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 704/HPTN 085 PSRT AE review are summarized in Table 10-1. Infusions may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the HVTN 704/HPTN 085 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of infusions are listed in Section 5.3.

Table 10-1 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	CRS action ^a	HVTN Core ^b action
SAE, related	Grade 4 or 5	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 704/HPTN 085 PSRT notification
SAE, related	Grade 3	E-mail and submit forms immediately	Prompt HVTN 704/HPTN 085 PSRT AE review to consider pause
AE ^c , related	Grade 4 or 3	Email and submit forms immediately	Prompt HVTN 704/HPTN 085 PSRT AE review to consider pause

^a Phone numbers and email addresses are found on the Protocol home page on the HVTN Members' site (<https://members.hvtn.org/protocols/hvtn704/HPTN085>).

^b HVTN CSS or HVTN Core designee

^c Does not include subjective reactogenicity symptoms (injection site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea).

For all safety pauses, HVTN Core notifies the HVTN 704/HPTN 085 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN and HPTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the NIAID DSMB.

Once a trial is paused, the HVTN 704/HPTN 085 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of infusions is appropriate, consulting the NIAID DSMB if necessary. HVTN Core notifies the participating HVTN and HPTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study infusions. Based on the HVTN 704/HPTN 085 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 704/HPTN 085 PSRT notification or prompt HVTN 704/HPTN 085 PSRT AE review is triggered, HVTN Core notifies the HVTN 704/HPTN 085 PSRT as soon as possible during working hours (US Pacific Time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 704/HPTN 085 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and an applicable RE protocol-related safety information (such as IND safety reports, notification of study product holds due to the pause rules, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 704/HPTN 085 PSRT (see Section 10.4.2).

10.4 Review of cumulative safety data

Routine safety review occurs at the start of enrollment and then throughout the study.

Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and include queries to the CRSs. Events are tracked by internal reports until resolution.

10.4.1 Daily review

Blinded daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 704/HPTN 085 PSRT AE review criteria.

10.4.2 Twice monthly review

During the infusion phase of the trial, the HVTN 704/HPTN 085 PSRT reviews clinical safety reports twice each month and conducts calls to review the data as appropriate. After the infusions and the final postinfusion safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 704/HPTN 085 PSRT. The HVTN CSS or HVTN Core designee reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

10.4.3 DSMB review of cumulative safety data

The DSMB will periodically review accumulating safety data. Prior to each such review, the SDMC will provide the DSMB with data as described in Section 4.9.1. Reports will be cumulative, generated from an up-to-date data file. Reports will show the data coded by treatment group; however, upon request of the DSMB, the SDMC will provide the Board with the actual treatment group.

10.5 Study termination

This study may be terminated early by NIAID upon recommendation by the DSMB, a pertinent national regulatory authority, Office for Human Research Protections (OHRP), or study product developer. In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

10.6 Social impact reporting

It is possible that participants' involvement in the study could result in social impacts. For example, a participant's involvement in the study could become known to others, and a social harm may result (ie, because participants could be perceived as being HIV infected or at "high risk" for HIV infection). Participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Alternatively, a social benefit may result (eg, a participant could feel good helping others).

Social harms are negative social impact events and social benefits are positive social impact events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. Social impacts will be collected and reported on CRFs during scheduled visits (see Appendix J through Appendix M). A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. While maintaining participant confidentiality, study sites may engage their Community Advisory Board (CAB) in exploring the social context surrounding instances of social harms to minimize the potential occurrence of such an impact.

11 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with Good Clinical Practice (GCP) (ICHe6), the HVTN and HPTN network-specific *Manuals of Operations*, and DAIDS Clinical Research Policies and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Ancillary studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the SSP.

11.1 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site should contact the participant first, and then notify the IRB/EC and any applicable RE of the matter as soon as possible.

12 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of clinical trials. The HVTN and HPTN (hereafter, referred to as the “Networks”) have addressed ethical concerns in the following ways:

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for preventing HIV infection, using methods that are scientifically rigorous and valid, and in accordance with GCP guidelines.
- Network scientists and operational staff incorporate the philosophies underlying major codes [139-141], declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV prevention clinical trials.
- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. CABs are required by DAIDS and supported at all Network research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines [142].
- Network clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
- The Networks require that all international Network sites lacking national plans for providing ART develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants will be referred to programs for ART provision when the appropriate criteria for starting ART are met. If a program is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.
- The Networks agree that appropriate referrals for access to PrEP and PEP should be provided according to national and/or local guidelines.
- The Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.
- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.
- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.

- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.
- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.
- The Networks recognize the importance of institutional review and values the role of in country IRBs, ECs, and any applicable REs as custodians responsible for ensuring the ethical conduct of research in each setting.

13 IRB/EC/RE review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs to ensure that certain requirements are satisfied on initial and continuing review of research (Title 45, Code of Federal Regulations (CFR), Part 46.111(a) 1-7; 21 CFR 56.111(a) 1-7). The following section highlights how this protocol addresses each of these research requirements. Each Network Investigator welcomes IRB/EC and any applicable RE questions or concerns regarding these research requirements.

This trial is being conducted in North America, South America, and Switzerland with funding from the US NIH. Due to this, the trial is subject to both US and local regulations and guidelines on the protection of human research subjects and ethical research conduct. Where there is a conflict in regulations or guidelines, the regulation or guideline providing the maximum protection of human research subjects will be followed.

In compliance with international and local (as appropriate) GCP, each research location has a locally based Principal Investigator (PI) who is qualified to conduct (and supervise the conduct of) the research; and the research addresses an important local health need for an HIV prevention method. In addition, the investigators take responsibility for the conduct of the study and the control of the study products, including obtaining all appropriate regulatory and ethical reviews of the research. Each participating site has a standard operating procedure for ensuring that participants have the necessary information to make a decision whether or not to consent to the research.

The sections below address each of the review concerns by IRBs/ECs and any applicable REs regarding how the research will be conducted.

13.1 Minimized risks to participants

45 CFR 46.111 (a) 1 and 21 CFR 56.111 (a) 1: Risks to subjects are minimized.

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants following study product administration and collecting information regarding side effects for several days following study product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product infusions, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use (for participants capable of becoming pregnant); and (f) providing safety monitoring.

13.2 Reasonable risk/benefit balance

45 CFR 46.111(a) 2 and 21 CFR 56.111(a) 2: Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a healthy participant are not as apparent as they would be in treatment protocols, where a study participant may be ill and may have exhausted all conventional treatment options. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

13.3 Equitable subject selection

45 CFR 46.111 (a) 3 and 21 CFR 56.111 (a) 3: Subject selection is equitable

This protocol has specific inclusion and exclusion criteria for investigators to follow in admitting participants into the protocol. Participants are selected because of these criteria and not because of positions of vulnerability or privilege. Investigators are required to maintain screening and enrollment logs to document volunteers who screened into and out of the protocol and for what reasons.

13.4 Appropriate informed consent

45 CFR 46.111 (a) 4 & 5 and 21 CFR 56.111 (a) 4 & 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section 7.1). Each site is provided training in informed consent by the Networks as part of its entering the respective Network. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

13.5 Adequate safety monitoring

45 CFR 46.111 (a) 6 and 21 CFR 56.111 (a) 6: There is adequate provision for monitoring the data collected to ensure the safety of subjects.

This protocol has extensive safety monitoring in place (Section 10). Safety is monitored daily by the HVTN CSS or HVTN Core designee and routinely by the HVTN 704/HPTN 085 PSRT. In addition, a DSMB periodically reviews study data.

13.6 Protect privacy/confidentiality

45 CFR 46.111 (a) 7 and 21 CFR 56.111 (a) 7: There are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term "privacy" concerns research participants or potential research participants as individuals whereas the term "confidentiality" is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see Appendix A). The privacy of participants is protected by assigning unique identifiers in place of the participant's name on study data and specimens. In the United States, research participants in Network protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data/Specimens with the Networks and each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

14 Version history

The Protocol Team may modify the original version of the protocol. Modifications are made to Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 704/HPTN 085 are described below.

Protocol history and modifications

Date: June 15, 2017

Protocol version: Version 3.0

Protocol modification: Full Protocol Amendment 2

- Item 1 Revised: Study duration and participant follow-up
- Item 2 Updated in Section 1.1: Protocol team membership
- Item 3 Updated in Sections 2.9, 2.9.3, 2.9.4, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 4 Revised in Section 4.9.3: *Monitoring for futility to assess PE*
- Item 5 Clarified in Section 5.1, *Inclusion criteria*: Transgender volunteer eligibility
- Item 6 Added in Section 5.1, *Inclusion criteria*: Hgb criterion adjustment for MTF transgender volunteers using feminizing hormones
- Item 7 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 8 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature
- Item 9 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation
- Item 10 Updated in Section 6.4 and Appendix A: Minimum infusion time
- Item 11 Added in Section 6.4, *Administration*: In-line filter set requirement
- Item 12 Clarified in Section 6.4, *Administration*: IV bag temperature equilibration and label weight
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 14 Updated in Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*: DAIDS AE grading table version and exceptions
- Item 15 Updated in Section 10.2, *Safety reporting*: URLs for referenced documents
- Item 16 Clarified in Section 10.2.2, *AE reporting*: Working hours for CSS or RML response
- Item 17 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*

- Item 18 Updated in Section 14: Version history
- Item 19 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 20 Corrected in Section 16: *Acronyms and abbreviations*
- Item 21 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 22 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 23 Added in Appendix B, *Approved birth control methods for transgender men (for sample informed consent form)*: Condom use and pregnancy testing
- Item 24 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoints
- Item 25 Updated in Appendices F through I: Assay locations, HVTN laboratory listings, and blood draw totals
- Item 26 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X
- Item 27 Removed in Appendices G and H: Footnote regarding whole blood for HIV diagnostics
- Item 28 Clarified in Appendices J and M: Provision of HIV test results
- Item 29 Added as Appendix N: Protocol signature page
- Item 30 Revised in Letter of Amendment 1 to Version 2.0: Interim safety and feasibility assessments
- Item 31 Corrected: Minor typographical, grammatical, and formatting errors

Date: December 14, 2016

Protocol version: Version 2.0

Protocol modification: Letter of Amendment 1

- Item 1 Revised in Section 1, *Overview* and Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*: Interim safety assessments
- Item 2 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

Date: July 19, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

- Item 1 Corrected in Section 1, *Overview*: Estimated total study duration
- Item 2 Added: Switzerland as study location
- Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil
- Item 4 Updated in Section 1.1: *Protocol team* membership
- Item 5 Revised: PrEP monitoring

- Item 6 Removed in Section 2.9.3, *HVTN 104*: Incorrect systemic reactogenicity rate
- Item 7 Clarified in Sections 4.9.1 and 10.4.3: Data reporting to DSMB
- Item 8 Clarified in Section 4.9.1.1, *Sequential monitoring for potential harm, non-efficacy, and high efficacy*: Caption to Figure 4-6
- Item 9 Added in Section 5.1, *Inclusion criteria*: Reference to SSP for clarification of transgender eligibility
- Item 10 Clarified in Section 5.2, *Exclusion criteria*: PSRT may permit exceptions to Exclusion criterion #4
- Item 11 Clarified in Section 6, *Study product preparation and administration*: Administration volumes, bag covers, and expiration prompts
- Item 12 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits* and Section 7.10, *Assessment of reactogenicity*: Recording and source documentation for reactogenicity events
- Item 14 Clarified in Section 7.3, *Enrollment and infusion visits*, and Appendices D, F, and J: STI testing
- Item 15 Clarified in Section 7.9, *Urine testing*: Follow-up to abnormal urine dipstick result at screening
- Item 16 Clarified in Appendix A, *Sample informed consent form*: VRC01 not being developed for sale
- Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants
- Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”
- Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling
- Item 21 Throughout protocol document: Minor errors corrected
- Item 22 Updated: Section 14, *Version history*

Date: March 9, 2016

Protocol version: 1.0

Protocol modification: Original protocol

15 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at <http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf>
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at <https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>
- Division of AIDS Protocol Registration Manual. Available at <https://www.niaid.nih.gov/sites/default/files/prmanual.pdf>
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1, dated March 2017. Available at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 704/HPTN 085 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 704/HPTN 085 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/publications/dgr/Pages/index.aspx>
- HVTN Lab Assay Algorithm (available upon request)
- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

- HVTN 704/HPTN 085 Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.
- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>
- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at <https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx>
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

See Section 17 for literature cited in the background and statistics sections of this protocol.

16 Acronyms and abbreviations

ACASI	audio computer assisted self-interview
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADCVI	antibody-dependent cellular viral inhibition
AIA	anti-idiotypic antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence intervals
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CRS*	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DSMB	(NIAID) Data and Safety Monitoring Board
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
GC	gonorrhea
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
IC ₅₀	inhibitory concentration (50%)
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LANL	Los Alamos National Laboratory
LC	Laboratory Center
LOC	Leadership and Operations Center
mAb	monoclonal antibody
MITT	modified intent-to-treat
MSM	men who have sex with men
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NICD	National Institute for Communicable Diseases (Johannesburg, South Africa)
NIH	US National Institutes of Health
NVITAL	NIAID Vaccine Immune T-Cell Antibody Laboratory
OC	Oversight Committee
PBMC	peripheral blood mononuclear cell
PE	prevention efficacy
PEP	postexposure prophylaxis
PI	Principal Investigator
PK	pharmacokinetic
PMTCT	prevention of mother-to-child (HIV) transmission
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
PYR	person year
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	(DAIDS) Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study specific procedures

STI	sexually transmitted infection
TasP	treatment as prevention
TCID ₅₀	tissue culture infectious dose (50%)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TG	transgender
tMLE	targeted maximum likelihood estimation
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VRC	Vaccine Research Center (NIAID)
VRP	Vaccine Research Program
WHO	World Health Organization

* CRSs were formerly referred to as HIV Vaccine Trial Units (HVTUs). Conversion to use of the term CRS is in process, and some HVTN documents may still refer to HVTUs.

17 Literature cited

1. UNAIDS. Report on the Global AIDS Epidemic, 2012 country progress reports. <http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/>. 2013. Last accessed: 2-20-2013
2. UNAIDS. Global Report: Report on the global AIDS epidemic 2013. **2013**;UNAIDS / JC2502/1/E.
3. WHO in partnership with UNICEF and UNAIDS. Global Report on HIV Treatment 2013: Results, Impact and Opportunities. **2014**.
4. UNAIDS. Local Epidemics Issues Brief. **2014**.
5. HIV/AIDS Fact Sheet. **11-2015**. <http://www.who.int/mediacentre/factsheets/fs360/en/>, accessed February 8, 2016.
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de BG, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **2011**;365:493-505.
7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* **2010**;363:2587-99.
8. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: Limitations to Treatment Safety and Efficacy: Adverse Effects of Antiretroviral Agents. <http://aidsinfo.nih.gov/guidelines>. 5-1-2014. Last accessed: 2-17-2015
9. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* **2012**;26:F13-F19.
10. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clin Infect Dis* **1992**;14:580-6.
11. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2006**;55:1-23.
12. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. *Curr Opin HIV AIDS* **2015**;10:129-34.

13. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* **1998**;102:531-7.
14. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, Connor EM, Losonsky GA. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics* **2010**;125:e35-e51.
15. Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective. *Int J Pediatr* **2014**;2014:571609.
16. Li Y, Migueles SA, Welcher B, Svehla K, Phogat A, Louder MK, Wu X, Shaw GM, Connors M, Wyatt RT, Mascola JR. Broad HIV-1 neutralization mediated by CD4-binding site antibodies. *Nat Med* **2007**;13:1032-4.
17. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarragona-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee DA, Manigart O, Karita E, Inwoley A, Jaoko W, Dehovitz J, Bekker LG, Pitisuttithum P, Paris R, Walker LM, Pognard P, Wrin T, Fast PE, Burton DR, Koff WC. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. *J Virol* **2009**;83:7337-48.
18. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, McKee K, O'Dell S, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science* **2010**;329:856-61.
19. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, Kwon YD, Scheid JF, Shi W, Xu L, Yang Y, Zhu J, Nussenzweig MC, Sodroski J, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science* **2010**;329:811-7.
20. Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, Wibmer CK, Puren A, DeCamp A, Gilbert PB, Wood B, Montefiori DC, Binley JM, Shaw GM, Haynes BF, Mascola JR, Morris L. Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. *J Virol* **2009**;83:8925-37.
21. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol* **2011**;85:4828-40.
22. Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez BM, Silacci C, Pinna D, Jarrossay D, Balla-Jhaghoorsingh S, Willems B, Zekveld MJ, Dreja H, O'Sullivan E, Pade C, Orkin C, Jeffs SA, Montefiori DC, Davis D, Weissenhorn W, McKnight A, Heeney JL, Sallusto F, Sattentau QJ, Weiss RA, Lanzavecchia A. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. *PLoS ONE* **2010**;5:e8805.

23. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, Wang SK, Ramos A, Chan-Hui PY, Moyle M, Mitcham JL, Hammond PW, Olsen OA, Phung P, Fling S, Wong CH, Phogat S, Wrin T, Simek MD, Koff WC, Wilson IA, Burton DR, Poignard P. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* **2011**;477:466-70.
24. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, Pietzsch J, Fenyo D, Abadir A, Velinzon K, Hurley A, Myung S, Boulad F, Poignard P, Burton DR, Pereyra F, Ho DD, Walker BD, Seaman MS, Bjorkman PJ, Chait BT, Nussenzweig MC. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science* **2011**;333:1633-7.
25. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, Wood B, Nathe C, Richman D, Tomaras GD, Bibollet-Ruche F, Robinson JE, Morris L, Shaw GM, Montefiori DC, Mascola JR. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. *J Virol* **2008**;82:11651-68.
26. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, Stamatatos L. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. *J Virol* **2009**;83:757-69.
27. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, Wu X, Seaman MS, Wrin T, Kwong PD, Wyatt RT, Mascola JR, Poignard P, Burton DR. PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. *J Virol* **2012**;86:4394-403.
28. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL, Lehrman JK, Priddy FH, Olsen OA, Frey SM, Hammond PW, Kaminsky S, Zamb T, Moyle M, Koff WC, Poignard P, Burton DR. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science* **2009**;326:285-9.
29. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, Phogat SK, Poignard P, Burton DR. A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. *PLoS Pathog* **2010**;6:e1001028.
30. McLellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, Louder R, Pejchal R, Sastry M, Dai K, O'Dell S, Patel N, Shahzad-ul-Hussan S, Yang Y, Zhang B, Zhou T, Zhu J, Boyington JC, Chuang GY, Diwanji D, Georgiev I, Kwon YD, Lee D, Louder MK, Moquin S, Schmidt SD, Yang ZY, Bonsignori M, Crump JA, Kapiga SH, Sam NE, Haynes BF, Burton DR, Koff WC, Walker LM, Phogat S, Wyatt R, Orwenyo J, Wang LX, Arthos J, Bewley CA, Mascola JR, Nabel GJ, Schief WR, Ward AB, Wilson IA, Kwong PD. Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature* **2011**;480:336-43.
31. Kong L, Lee JH, Doores KJ, Murin CD, Julien JP, McBride R, Liu Y, Marozsan A, Cupo A, Klasse PJ, Hoffenberg S, Caulfield M, King CR, Hua Y, Le KM, Khayat R, Deller MC, Clayton T, Tien H, Feizi T, Sanders RW, Paulson JC, Moore JP, Stanfield RL,

- Burton DR, Ward AB, Wilson IA. Supersite of immune vulnerability on the glycosylated face of HIV-1 envelope glycoprotein gp120. *Nat Struct Mol Biol* **2013**;20:796-803.
32. Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, Imamichi H, Bailer RT, Chakrabarti B, Sharma SK, Alam SM, Wang T, Yang Y, Zhang B, Migueles SA, Wyatt R, Haynes BF, Kwong PD, Mascola JR, Connors M. Broad and potent neutralization of HIV-1 by a gp41-specific human antibody. *Nature* **2012**;491:406-12.
 33. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat Med* **2009**;15:866-70.
 34. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. *Curr Opin Immunol* **2010**;22:358-66.
 35. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, Kaufmann DE, McElrath MJ, Nussenzweig MC, Pulendran B, Scanlan CN, Schief WR, Silvestri G, Streeck H, Walker BD, Walker LM, Ward AB, Wilson IA, Wyatt R. A Blueprint for HIV Vaccine Discovery. *Cell Host Microbe* **2012**;12:396-407.
 36. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. *Proc Natl Acad Sci U S A* **2005**;102:14943-8.
 37. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **2012**;37:412-25.
 38. Georgiev IS, Gordon JM, Zhou T, Kwong PD. Elicitation of HIV-1-neutralizing antibodies against the CD4-binding site. *Curr Opin HIV AIDS* **2013**;8:382-92.
 39. Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, Imamichi H, Doria-Rose N, Hoxie JA, Connors M, Shaw GM, Wyatt RT, Mascola JR. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol* **2012**;86:5844-56.
 40. Shibata R, Igarashi T, Haigwood N, Buckler-White A, Ogert R, Ross W, Willey R, Cho MW, Martin MA. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat Med* **1999**;5:204-10.
 41. Baba TW, Liska V, Hofmann-Lehmann R, Vlasak J, Xu W, Ayehunie S, Cavacini LA, Posner MR, Katinger H, Stiegler G, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Lu Y, Wright JE, Chou TC, Ruprecht RM. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat Med* **2000**;6:200-6.
 42. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Jiang S, Li PL, Baba TW, Montefiori DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Ruprecht RM. Postnatal pre- and postexposure passive immunization strategies: protection of neonatal macaques against oral simian-human immunodeficiency virus challenge. *J Med Primatol* **2002**;31:109-19.

43. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
44. Hessel AJ, Rakasz EG, Poignard P, Hangartner L, Landucci G, Forthal DN, Koff WC, Watkins DI, Burton DR. Broadly neutralizing human anti-HIV antibody 2G12 is effective in protection against mucosal SHIV challenge even at low serum neutralizing titers. *PLoS Pathog* **2009**;5:e1000433.
45. Hessel AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nat Med* **2009**;15:951-4.
46. Moldt B, Rakasz EG, Schultz N, Chan-Hui PY, Swiderek K, Weisgrau KL, Piaskowski SM, Bergman Z, Watkins DI, Poignard P, Burton DR. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. *Proc Natl Acad Sci U S A* **2012**;109:18921-5.
47. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, McKee K, Kong WP, Shi W, Chen X, Todd JP, Letvin NL, Huang J, Nason MC, Hoxie JA, Kwong PD, Connors M, Rao SS, Mascola JR, Nabel GJ. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. *Sci Transl Med* **2014**;6:243ra88.
48. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, Zeng M, Schmidt SD, Todd JP, Penzak SR, Saunders KO, Nason MC, Haase AT, Rao SS, Blumberg RS, Mascola JR, Nabel GJ. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature* **2014**;514:642-5.
49. Rudicell RS, Kwon YD, Ko SY, Pegu A, Louder MK, Georgiev IS, Wu X, Zhu J, Boyington JC, Chen X, Shi W, Yang ZY, Doria-Rose NA, McKee K, O'Dell S, Schmidt SD, Chuang GY, Druz A, Soto C, Yang Y, Zhang B, Zhou T, Todd JP, Lloyd KE, Eudailey J, Roberts KE, Donald BR, Bailer RT, Ledgerwood J, Mullikin JC, Shapiro L, Koup RA, Graham BS, Nason MC, Connors M, Haynes BF, Rao SS, Roederer M, Kwong PD, Mascola JR, Nabel GJ. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* **2014**;88:12669-82.
50. Florese RH, Demberg T, Xiao P, Kuller L, Larsen K, Summers LE, Venzon D, Cafaro A, Ensoli B, Robert-Guroff M. Contribution of nonneutralizing vaccine-elicited antibody activities to improved protective efficacy in rhesus macaques immunized with Tat/Env compared with multigenic vaccines. *J Immunol* **2009**;182:3718-27.
51. Forthal DN, Landucci G, Phan TB, Becerra J. Interactions between natural killer cells and antibody Fc result in enhanced antibody neutralization of human immunodeficiency virus type 1. *J Virol* **2005**;79:2042-9.
52. Asmal M, Sun Y, Lane S, Yeh W, Schmidt SD, Mascola JR, Letvin NL. Antibody-dependent cell-mediated viral inhibition emerges after simian immunodeficiency virus

SIVmac251 infection of rhesus monkeys coincident with gp140-binding antibodies and is effective against neutralization-resistant viruses. *J Virol* **2011**;85:5465-75.

53. Tudor D, Derrien M, Diomedea L, Drillet AS, Houimel M, Moog C, Reynes JM, Lopalco L, Bomsel M. HIV-1 gp41-specific monoclonal mucosal IgAs derived from highly exposed but IgG-seronegative individuals block HIV-1 epithelial transcytosis and neutralize CD4(+) cell infection: an IgA gene and functional analysis. *Mucosal Immunol* **2009**;2:412-26.
54. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, Shapiro L, Mascola JR. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature* **2014**;509:55-62.
55. Pancera M, Shahzad-ul-Hussan S, Doria-Rose NA, McLellan JS, Bailer RT, Dai K, Loesgen S, Louder MK, Staupe RP, Yang Y, Zhang B, Parks R, Eudailey J, Lloyd KE, Blinn J, Alam SM, Haynes BF, Amin MN, Wang LX, Burton DR, Koff WC, Nabel GJ, Mascola JR, Bewley CA, Kwong PD. Structural basis for diverse N-glycan recognition by HIV-1-neutralizing V1-V2-directed antibody PG16. *Nat Struct Mol Biol* **2013**;20:804-13.
56. Zhou T, Lynch RM, Chen L, Acharya P, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, McKee K, O'Dell S, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, Peng HP, Yang AS, Mullikin JC, Gray MD, Stamatatos L, Burton DR, Koff WC, Cohen MS, Haynes BF, Casazza JP, Connors M, Corti D, Lanzavecchia A, Sattentau QJ, Weiss RA, West AP, Jr., Bjorkman PJ, Scheid JF, Nussenzweig MC, Shapiro L, Mascola JR, Kwong PD. Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors. *Cell* **2015**;161:1280-92.
57. Chuang GY, Acharya P, Schmidt SD, Yang Y, Louder MK, Zhou T, Kwon YD, Pancera M, Bailer RT, Doria-Rose NA, Nussenzweig MC, Mascola JR, Kwong PD, Georgiev IS. Residue-level prediction of HIV-1 antibody epitopes based on neutralization of diverse viral strains. *J Virol* **2013**;87:10047-58.
58. Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, Denham SA, Heil ML, Kasolo F, Musonda R, Hahn BH, Shaw GM, Korber BT, Allen S, Hunter E. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* **2004**;303:2019-22.
59. Wilen CB, Parrish NF, Pfaff JM, Decker JM, Henning EA, Haim H, Petersen JE, Wojcechowskyj JA, Sodroski J, Haynes BF, Montefiori DC, Tilton JC, Shaw GM, Hahn BH, Doms RW. Phenotypic and immunologic comparison of clade B transmitted/founder and chronic HIV-1 envelope glycoproteins. *J Virol* **2011**;85:8514-27.

60. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, Karon J, Brookmeyer R, Kaplan EH, McKenna MT, Janssen RS. Estimation of HIV incidence in the United States. *JAMA* **2008**;300:520-9.
61. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, Lin LS, An Q, Mermin J, Lansky A, Hall HI. Estimated HIV incidence in the United States, 2006-2009. *PLoS ONE* **2011**;6:e17502.
62. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, Koblin BA, Mayer KH, Buchbinder SP. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PLoS ONE* **2012**;7:e50522.
63. Beyrer C, Baral SD, van GF, Goodreau SM, Chariyalertsak S, Wirtz AL, Brookmeyer R. Global epidemiology of HIV infection in men who have sex with men. *Lancet* **2012**;380:367-77.
64. Federal Office of Public Health (FOPH) Public Health Directorate, Swiss Confederation. Factsheet on HIV and AIDS in Switzerland 2014.
http://www.bag.admin.ch/hiv_aids/05464/12908/12909/12913/index.html?lang=en. 5-19-2015. Last accessed: 6-22-2016
65. Centers for Disease Control and Prevention. Diagnosis of HIV infection in the United States and dependent areas, 2013. HIV Surveillance Report, 2013; Vol. 25.
<http://www.cdc.gov/hiv/library/reports/surveillance/>. 2015. Last accessed: 5-13-2015
66. Centers for Disease Control and Prevention. Estimates HIV incidence in the United States, 2007-2010. HIV Surveillance Supplemental Report 2012:17(No. 4).
<http://www.cdc.gov/hiv/library/reports/surveillance/index.html>. 12-2-2015. Last accessed: 5-13-2015
67. Koblin BA, Mayer KH, Eshleman SH, Wang L, Mannheimer S, Del RC, Shoptaw S, Magnus M, Buchbinder S, Wilton L, Liu TY, Cummings V, Piwowar-Manning E, Fields SD, Griffith S, Elharrar V, Wheeler D. Correlates of HIV acquisition in a cohort of Black men who have sex with men in the United States: HIV prevention trials network (HPTN) 061. *PLoS ONE* **2013**;8:e70413.
68. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, Salazar LF, Frew P, Wingood G, Diclemente R, Del RC, Mulligan M, Sanchez TH. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. *PLoS ONE* **2014**;9:e90514.
69. World Medical Association. Ethical Principles for Medical Research Involving Human Subjects, Note of Clarification on Paragraph 29. **2002**.
70. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* **2000**;283:2701-11.
71. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. *N Engl J Med* **2001**;345:915-9.
72. Ng CT, Jaworski JP, Jayaraman P, Sutton WF, Delio P, Kuller L, Anderson D, Landucci G, Richardson BA, Burton DR, Forthal DN, Haigwood NL. Passive neutralizing antibody

controls SHIV viremia and enhances B cell responses in infant macaques. *Nat Med* **2010**;16:1117-9.

73. Lynch RM, Wong P, Tran L, O'Dell S, Nason MC, Li Y, Wu X, Mascola JR. HIV-1 fitness cost associated with escape from the VRC01 class of CD4 binding site neutralizing antibodies. *J Virol* **2015**;89:4201-13.
74. Gilbert PB, Grove D, Gabriel E, Huang Y, Gray G, Hammer SM, Buchbinder SP, Kublin J, Corey L, Self SG. A Sequential Phase 2b Trial Design for Evaluating Vaccine Efficacy and Immune Correlates for Multiple HIV Vaccine Regimens. *Stat Commun Infect Dis* **2011**;3.
75. Kamb ML, Fishbein M, Douglas JM, Jr., Rhodes F, Rogers J, Bolan G, Zenilman J, Hoxworth T, Malotte CK, Iatesta M, Kent C, Lentz A, Graziano S, Byers RH, Peterman TA. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA* **1998**;280:1161-7.
76. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* **2014**;14:820-9.
77. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, Nardone A, Fisher M, McOwan A, Phillips AN, Johnson AM, Gazzard B, Gill ON. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* **2015**.
78. McCormack S, Dunn D. Pragmatic open-label randomized trial of preexposure prophylaxis: The PROUD study (Abstract 22LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
79. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On demand PrEP with Oral TDF-FTC in MSM: Results of the ANRS Ipergay trial (Abstract 23LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
80. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaugerre C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Preau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Dore V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* **2015**;373:2237-46.
81. Centers for Disease Control and Prevention. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex With Men.

<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm>. 1-28-2011. Last accessed: 4-10-2015

82. World Health Organization. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. July 2012. **2012**.
83. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: A Clinical Practice Guideline. **2014**.
84. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: Clinical Providers' Supplement. 2014. US Centers for Disease Control and Prevention.
85. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach. <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>. 6-30-2013. Last accessed: 2-2-2015
86. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. **2015**.
87. Liu AY, Cohen SE, Vittinghoff E, Anderson PL, Doblecki-Lewis S, Bacon O, Chege W, Postle BS, Matheson T, Amico KR, Liegler T, Rawlings MK, Trainor N, Blue RW, Estrada Y, Coleman ME, Cardenas G, Feaster DJ, Grant R, Philip SS, Elion R, Buchbinder S, Kolber MA. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. *JAMA Intern Med* **2015**;1-11.
88. Hoagland B, Veloso V, De Boni R, Madruga J, Kallas E, Fernandes N, Moreira R, Liu A, Grinsztejn B, PrEP Brasil Study Team. Pre-exposure prophylaxis (PrEP) uptake and associated factors among MSM and TGW in the PrEP Brasil demonstration project (TUAC0205LB) . IAS 2015, 8th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 19-22 July 2015, Vancouver, Canada, **2015**
89. Dawson L, Garner S, Anude C, Ndebele P, Karuna S, Holt R, Broder G, Handibode J, Hammer SM, Sobieszczyk ME. Testing the waters: Ethical considerations for including PrEP in a phase IIb HIV vaccine efficacy trial. *Clin Trials* **2015**;12:394-402.
90. Fuchs JD, Sobieszczyk ME, Madenwald T, Grove D, Karuna ST, Andrasik M, Sherwat A, Broder G, Mayer K, Koblin B, Hammer S. Intentions to Use Preexposure Prophylaxis Among Current Phase 2B Preventive HIV-1 Vaccine Efficacy Trial Participants. *J Acquir Immune Defic Syndr* **2013**;63:259-62.
91. Volk JE, Marcus JL, Phengrasamy T, Blechinger D, Nguyen DP, Follansbee S, Hare CB. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. *Clin Infect Dis* **2015**;61:1601-3.
92. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, Gupta S, Herzyk D, Hurst C, Ivens IA, Kawabata T, Maier C, Mounho B, Rup B, Shankar G, Smith H, Thomas P, Wierda D. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol* **2009**;54:164-82.

93. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* **2004**;93:2645-68.
94. Li Y, O'Dell S, Walker LM, Wu X, Guenaga J, Feng Y, Schmidt SD, McKee K, Louder MK, Ledgerwood JE, Graham BS, Haynes BF, Burton DR, Wyatt RT, Mascola JR. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *J Virol* **2011**;85:8954-67.
95. Haynes BF, Fleming J, St Clair EW, Katinger H, Stiegler G, Kunert R, Robinson J, Searce RM, Plonk K, Staats HF, Ortel TL, Liao HX, Alam SM. Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* **2005**;308:1906-8.
96. Mascola JR, Lewis MG, Stiegler G, Harris D, VanCott TC, Hayes D, Louder MK, Brown CR, Sapan CV, Frankel SS, Lu Y, Robb ML, Katinger H, Birx DL. Protection of Macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol* **1999**;73:4009-18.
97. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, Beary H, Hayes D, Frankel SS, Birx DL, Lewis MG. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat Med* **2000**;6:207-10.
98. Mascola JR. Defining the protective antibody response for HIV-1. *Curr Mol Med* **2003**;3:209-16.
99. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
100. Parren PW, Marx PA, Hessel AJ, Luckay A, Harouse J, Cheng-Mayer C, Moore JP, Burton DR. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* **2001**;75:8340-7.
101. Sadjadpour R, Donau OK, Shingai M, Buckler-White A, Kao S, Strebel K, Nishimura Y, Martin MA. Emergence of gp120 V3 variants confers neutralization resistance in an R5 simian-human immunodeficiency virus-infected macaque elite neutralizer that targets the N332 glycan of the human immunodeficiency virus type 1 envelope glycoprotein. *J Virol* **2013**;87:8798-804.
102. Gautam R, Nishimura Y, Lee WR, Donau O, Buckler-White A, Shingai M, Sadjadpour R, Schmidt SD, LaBranche CC, Keele BF, Montefiori D, Mascola JR, Martin MA. Pathogenicity and mucosal transmissibility of the R5-tropic simian/human immunodeficiency virus SHIV(AD8) in rhesus macaques: implications for use in vaccine studies. *J Virol* **2012**;86:8516-26.
103. Shingai M, Donau OK, Plishka RJ, Buckler-White A, Mascola JR, Nabel GJ, Nason MC, Montefiori D, Moldt B, Poignard P, Diskin R, Bjorkman PJ, Eckhaus MA, Klein F, Mouquet H, Cetrulo Lorenzi JC, Gazumyan A, Burton DR, Nussenzweig MC, Martin MA, Nishimura Y. Passive transfer of modest titers of potent and broadly neutralizing

anti-HIV monoclonal antibodies block SHIV infection in macaques. *J Exp Med* **2014**;211:2061-74.

104. Hessel AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. Fc receptor but not complement binding is important in antibody protection against HIV. *Nature* **2007**;449:101-4.
105. Saunders KO, Pegu A, Georgiev IS, Zeng M, Joyce MG, Yang ZY, Ko SY, Chen X, Schmidt SD, Haase AT, Todd JP, Bao S, Kwong PD, Rao SS, Mascola JR, Nabel GJ. Sustained Delivery of a Broadly Neutralizing Antibody in Nonhuman Primates Confers Long-Term Protection against Simian/Human Immunodeficiency Virus Infection. *J Virol* **2015**;89:5895-903.
106. Lynch RM, Boritz E, Coates EE, DeZure A, Madden P, Costner P, Enama ME, Plummer S, Holman L, Hendel CS, Gordon I, Casazza J, Conan-Cibotti M, Migueles SA, Tressler R, Bailer RT, McDermott A, Narpala S, O'Dell S, Wolf G, Lifson JD, Freemire BA, Gorelick RJ, Pandey JP, Mohan S, Chomont N, Fromentin R, Chun TW, Fauci AS, Schwartz RM, Koup RA, Douek DC, Hu Z, Capparelli E, Graham BS, Mascola JR, Ledgerwood JE. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. *Sci Transl Med* **2015**;7:319ra206.
107. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, DeZure A, Lynch RM, Gordon I, Plummer S, Hendel CS, Pegu A, Conan-Cibotti M, Sitar S, Bailer RT, Narpala S, McDermott A, Louder M, O'Dell S, Mohan S, Pandey JP, Schwartz RM, Hu Z, Koup RA, Capparelli E, Mascola JR, Graham BS. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol* **2015**;182:289-301.
108. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* **2010**;9:325-38.
109. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol* **2009**;5:499-521.
110. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* **2010**;14:E10-E21.
111. World Health Organization. Policy Brief: Pre-exposure prophylaxis (PrEP): WHO expands recommendation on oral pre-exposure prophylaxis of HIV infection (PrEP). **2015**.
112. Rosenbaum P. The consequences of adjustment for a concomitant variable that has been affected by the treatment. *Journal of the Royal Statistical Society, Series A (General)* **1984**;147:656-66.
113. Joffe MM, Greene T. Related causal frameworks for surrogate outcomes. *Biometrics* **2009**;65:530-8.
114. Follmann D. Augmented designs to assess immune response in vaccine trials. *Biometrics* **2006**;62:1161-9.

115. Gilbert PB, Hudgens MG. Evaluating candidate principal surrogate endpoints. *Biometrics* **2008**;64:1146-54.
116. Huang Y, Gilbert PB, Wolfson J. Design and estimation for evaluating principal surrogate markers in vaccine trials. *Biometrics* **2013**;69:301-9.
117. Rida W, Fast P, Hoff R, Fleming T. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol* **1997**;16:195-203.
118. Juraska, M, Grove, D, Yu, X, and Gilbert, PG. seqDesign: Simulation and Group Sequential Monitoring of Randomized Two-Stage Treatment Efficacy Trials with Time-to-Event Endpoints. R package version 1.1. <http://CRAN.R-project.org/package=seqDesign>. 4-27-2015. Last accessed: 5-15-2015
119. Berger RL, Boos DD. P values maximized over a confidence set for the nuisance parameter. *Journal of the American Statistical Association* **1994**;89:1012-6.
120. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials* **2010**;7:197-208.
121. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* **2013**;369:2083-92.
122. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* **1983**;39:499-503.
123. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data (Second Edition)*. John Wiley & Sons, Inc., **2002**.
124. Moore K, van der Laan M. Application of time-to-event methods in the assessment of safety in clinical trials. U. C. Berkeley Division of Biostatistics Working Paper Series, Paper 248. 2009.
125. van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. Springer, **2011**.
126. Gilbert PB, Wei LJ, Kosorok MR, Clemens JD. Simultaneous inferences on the contrast of two hazard functions with censored observations. *Biometrics* **2002**;58:773-80.
127. Edlefsen P, Magaret C, Poon A, Matsen I, Eller L, Tovanabutra S, Chopera D, Labuschagne P, Warth C, Holzman T, Rossenkahn R, Abrahams M-R, Logan M, Anthony C, Botha G, Matten D, Nitayaphan S, Rono K, Sekiziyivu A, Ndabambi N, Travers S, Michael N, Williamson C, Robb N, Gilbert P. Systematic evaluation of HIV infection time and founder inferences using SGA and Illumina sequences . Keystone Symposia on Molecular and Cellular Biology, HIV Vaccines (X8), Olympic Valley, California, USA, March 20-24, 2016, **2016**

128. Crooks GE, Hon G, Chandonia JM, Brenner SE. WebLogo: a sequence logo generator. *Genome Res* **2004**;14:1188-90.
129. Schneider TD, Stephens RM. Sequence logos: a new way to display consensus sequences. *Nucleic Acids Res* **1990**;18:6097-100.
130. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, Sinangil F, D'Souza P, Rodriguez-Chavez IR, DeCamp A, Giganti M, Berman PW, Self SG, Montefiori DC. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. *J Infect Dis* **2010**;202:595-605.
131. Montefiori DC. Measuring HIV neutralization in a luciferase reporter gene assay. *Methods Mol Biol* **2009**;485:395-405.
132. Todd CA, Greene KM, Yu X, Ozaki DA, Gao H, Huang Y, Wang M, Li G, Brown R, Wood B, D'Souza MP, Gilbert P, Montefiori DC, Sarzotti-Kelsoe M. Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells. *J Immunol Methods* **2012**;375:57-67.
133. Ozaki DA, Gao H, Todd CA, Greene KM, Montefiori DC, Sarzotti-Kelsoe M. International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials. *PLoS ONE* **2012**;7:e30963.
134. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodhi N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Masse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2015**;372:509-18.
135. Fogel JM, Wang L, Parsons TL, Ou SS, Piwowar-Manning E, Chen Y, Mudhune VO, Hosseinipour MC, Kumwenda J, Hakim JG, Chariyalertsak S, Panchia R, Sanne I, Kumarasamy N, Grinsztejn B, Makhema J, Pilotto J, Santos BR, Mayer KH, McCauley M, Gamble T, Bumpus NN, Hendrix CW, Cohen MS, Eshleman SH. Undisclosed antiretroviral drug use in a multinational clinical trial (HIV Prevention Trials Network 052). *J Infect Dis* **2013**;208:1624-8.
136. Marzinke MA, Clarke W, Wang L, Cummings V, Liu TY, Piwowar-Manning E, Breaud A, Griffith S, Buchbinder S, Shoptaw S, Del RC, Magnus M, Mannheimer S, Fields SD, Mayer KH, Wheeler DP, Koblin BA, Eshleman SH, Fogel JM. Nondisclosure of HIV status in a clinical trial setting: antiretroviral drug screening can help distinguish between newly diagnosed and previously diagnosed HIV infection. *Clin Infect Dis* **2014**;58:117-20.
137. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* **2013**;29:384-90.
138. Bushman LR, Kiser JJ, Rower JE, Klein B, Zheng JH, Ray ML, Anderson PL. Determination of nucleoside analog mono-, di-, and tri-phosphates in cellular matrix by

solid phase extraction and ultra-sensitive LC-MS/MS detection. J Pharm Biomed Anal **2011**;56:390-401.

139. UNAIDS. Ethical considerations in biomedical HIV prevention trials. **2007**.
140. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. **1979**.
141. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics **2002**;17-23.
142. UNAIDS/JC1853E (Second edition J2. Good participatory practice: Guidelines for biomedical HIV prevention trials. 2011.

Appendix A Sample informed consent form

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test the antibody called VRC01 against HIV. HIV is the virus that causes AIDS. Antibodies are one of the natural ways the body fights infection. Researchers can also make antibodies in laboratories and give them to people intravenously (with an IV). We will tell you more about this procedure below. This has been done successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 2700 people will take part in this study at multiple sites in North America, South America, and Switzerland. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

In addition, a similar study will be done with 1500 women in sub-Saharan Africa.

1. We are doing this study to answer several questions.

- Is the antibody safe to give to people?
- Are people able to take the antibody without becoming too uncomfortable?
- Does the antibody lower people's chances of getting infected with HIV?
- If the antibody does lower people's chances of getting infected with HIV, how much of it is needed to provide protection from HIV?

2. The antibody cannot give you HIV.

It is impossible for the antibody to give you HIV. Also, it cannot cause you to give HIV to someone else. However, we do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. The antibody is experimental.

The antibody being tested is called VRC-HIVMAB060-00-AB. It is an antibody against the HIV virus. From here on, we will call it VRC01 or the antibody. It is an experimental product. That means we do not know whether the antibody will be safe to use in people, or whether it will work to prevent HIV infection. This antibody is used only in research studies.

VRC01 was developed by the Vaccine Research Center at the US National Institutes of Health (NIH).

In laboratory and animal studies, VRC01 attached to and prevented infection by many strains of HIV viruses from around the world. We do not know if antibodies can prevent HIV infection when they are given to people. This study is designed to help us answer that question. At this time there are no plans to make VRC01 for sale.

Risks of VRC01 antibody:

As of April 2017, VRC01 has been given to people in 12 clinical studies in the United States, Peru, Brazil, Switzerland, and in sub-Saharan Africa. In these studies, more than 1800 adults and 33 infants have gotten VRC01 or a placebo (a liquid with no antibody in it).

Many of these studies are still going on and we don't know which people got VRC01 and which got a placebo. In early trials, more than 100 people got VRC01 and it did not make them too uncomfortable or cause serious health problems. After receiving the antibody, most people said that they had mild pain, itching, or redness where the antibody was given to them. Of these people, some said they felt like they had the flu after getting the antibody, but that this feeling lasted a few hours at most.

In a previous study, one person who got a VRC01 injection had a rash. One person had a brief fainting spell several hours after getting a VRC01 infusion. To be safe, no more injections or infusions were given to these people. Some participants had mild body discomfort, muscle pain, or joint pain after getting the VRC01 antibody.

VRC01 may have other side effects that we do not know about yet.

General risks of antibodies:

Antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain.

Rarely, some antibodies have caused serious reactions. These reactions may be life-threatening. Please tell us if you have ever had any of the following reactions.

- One type of serious reaction, called anaphylaxis, may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face.

- A second type of serious reaction, called serum sickness, may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath.

Rarely, antibodies licensed for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with the VRC01 antibody.

When antibodies are given to a person by IV they do not last in the body more than a few months. Any antibody given to you in this study should be gone from your body several months after your last dose.

Joining the study

4. It is completely up to you whether or not to join the study.

Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

If you join this study, you may not be allowed to join some other kinds of HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Also during the study, you should not donate blood or tissue.

If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. If you want to join the study, we will screen you to see if you are eligible.

Screening involves a physical exam, HIV test and health history. A physical exam may include, but is not limited to:

- Checking your weight, temperature and blood pressure
- Looking in your mouth and throat
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also ask you about medications you are taking. We will ask you about behaviors that might put

you at risk for getting HIV. If you could become pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

(Sites: adapt the following section so it is applicable to the care available at your site)

6. If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.

- For the care that we cannot give, we will explain how we will help you get care elsewhere.

For health problems that are unrelated to the study, we will not pay for care.

7. If you could become pregnant, you must agree to use birth control to join this study.

Site: If you want to include Appendix B, Approved birth control methods for transgender men (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the antibody could affect the developing baby. You must agree to use effective birth control from 21 days before you first receive the antibody until your last scheduled clinic visit (about 1¾ years after your first IV). We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. You will come to the clinic for scheduled visits about [#] times over about 2 years.

The study will require [#] visits. That is about 1 visit every month for about the first 1½ years and then about every 2 months after that. You may have to come for more visits if you have a lab or health issue.

Visits can last from about [#] minutes to [#] hours. The IV procedure can take about 15 minutes to an hour.

We may contact you after the main study ends (for example, to tell you about the study results).

9. We will give you [Site: Insert compensation] for each study visit you complete.

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, birth control costs for participants capable of becoming pregnant).

Following paragraph for US sites only:

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

You do not have to pay anything to be in this study.

10. We will give you either the antibody or a placebo.

Not everyone in this study will get the VRC01 antibody. Some people will get a placebo, a liquid that does not contain any antibody. We will compare the results from people who got the placebo with results from people who got the VRC01 antibody. In this study, the placebo is sterile salt water, which is found naturally in the body.

There are three groups in this study. One group will get a lower dose of the VRC01 antibody, one group will get a higher dose, and one group will get the placebo. The high and low doses of the antibody will be adjusted for your body weight. We will weigh you to determine the amount you will get.

Overall, if you join this study, you have a 2-in-3 chance of getting the study antibody.

Site: Modify the randomization metaphor in the next sentence as appropriate to your local culture.

Whether you get the low dose of the antibody, the high dose of the antibody, or the placebo is completely random, like flipping a coin.

We have no say in whether you get the antibody or the placebo. If you get the antibody, we have no say in which dose you get. We will not know what you are getting, and neither will you. Only the pharmacist at this clinic will have this information while the study is going on.

You will have to wait until everyone completes their final study visits to find out whether you got the antibody or the placebo. This could be up to about 5 years. But, if you have a serious medical problem and need to know what you got before the end of the study, we can tell you.

If it is found to be effective, there are no plans to give the antibody to participants after the study. Instead, we will use what is learned in this study to determine if the antibody would be useful to prevent HIV, how the antibody could be improved, and how to produce it for wide public use.

11. We will give you the antibody or placebo on a schedule.

You will get the VRC01 antibody or the placebo during the study by IV. To get an IV, a needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small bag of fluid that contains the antibody or placebo. An IV pump controls how

fast the fluid drips from the bag, through the tube, and into your vein. There will be 10 IV procedures, one IV every 8 weeks. Other study visits will not include IVs.

Infusion schedule



Group	Dose	First IV	Weeks after first IV								
			Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72
Group 1	Lower dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 2	Higher dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 3	Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

You will have to wait in the clinic for about 30 minutes after the first IV to see if there are any problems. You probably will not have to wait after the IVs at the rest of the IV visits. After each IV visit, for that night and for three more days, you will be asked to keep track of how you feel. To help you do this, we can give you tools and show you how to use them. We will ask you the ways we can contact you. We will contact you about 3 days after each IV visit to ask how you have been feeling. Contact the clinic staff if you have any concerns after getting an infusion. If you have a problem, we will continue to check on you until it goes away

12. In addition to giving you the antibody or placebo, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you could become pregnant;
- Ask questions about your health, including medications you may be taking;
- Ask questions about any personal problems or benefits you may have from being in the study; and
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 30 mL and 180 mL (6 teaspoons to $\frac{3}{4}$ cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, “To compare, people who donate blood in the US can give a total of about 500 mL in an 8-week period.”). Modify the example for cultural relevance and alter blood volumes as necessary.

*Site: Insert the **first** table in Appendix D, Table of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.*

We will be looking for side effects.

We will do blood tests for syphilis and urine tests for gonorrhea and chlamydia. We will also test for gonorrhea and chlamydia using rectal swabs. We will do these tests at 4 visits. We will also test for gonorrhea and chlamydia using mouth and throat swabs at your first infusion visit. We will explain what each of these infections is. If the tests show that you have an infection, we will provide counseling and will help you get treatment. This study cannot pay for that treatment. *[Site: Revise preceding sentence if you provide or pay for STI treatment.]*

We will review the results of the procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. We will test your samples for this study.

We will send your samples (without your name) to labs approved by the HVTN and the HPTN for this study. These labs are located in the United States, South America, and South Africa. The samples will be tested to:

- measure how much antibody is in your blood,
- see how your immune system responds to the antibody, and
- see if there is antiretroviral medicine (also called ART/ARV) in your blood.

Researchers may also do genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The differences in people's genes can help explain why some people get a disease while others do not. These types of genetic tests involve only some of your genes, not all of your genes (your genome). The researchers will study the genes related to the immune system and HIV and those that affect how people get HIV.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the antibody.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

Tests done on your samples are for research purposes only. The labs will not give the results to you or this clinic, and the results will not become part of your study record.

When your samples are no longer needed for this study, the HVTN will continue to store them.

Site: Delete next section if using separate consent for use of samples and information in other studies

14. When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This section gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

Do I have to agree? No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

Where are the samples stored? Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

How long will the samples be stored? There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

Will I benefit from allowing my samples to be used in other studies? Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

How do other researchers get my samples and information? When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher’s location.

What information is shared with other researchers? The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

15. We will counsel you on reducing your risk for HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior and drug use. We will provide you with condoms and lubricant. We will talk with you about ways of lowering your risk of getting HIV. We will help you develop a risk reduction plan. Some topics we may discuss include:

- What you think causes risky behavior for you, and
- Ways to avoid getting HIV or giving it to someone else

[Site: adjust the language in this paragraph about PrEP provision to meet local availability.] These methods may include not having sex, using condoms, or other behavior changes. We will talk about new methods of HIV prevention, including pre-exposure prophylaxis (PrEP) with a drug called Truvada, and help you decide which of these methods is right for you.

[Site: The text in the next two paragraphs applies to US sites only. Sites should adjust the language in this paragraph to meet local PrEP availability.] Gilead Sciences, Inc. (the maker of Truvada) has agreed to provide Truvada as PrEP to study participants in HVTN 704/HPTN 085 through a mail order pharmacy. If you are interested, we can give you more information about this program. We can refer you to health care providers who can prescribe PrEP either through the Gilead program or from a different source.

If you accept the Gilead Sciences, Inc. offer to receive Truvada as PrEP during the study, the following study data will be shared with Gilead Sciences, Inc.:

- Your study ID code number
- Information such as your age, sex at birth, and gender
- Your past and present health conditions

Truvada has been shown to substantially lower people's risk of getting HIV when taken every day. The US FDA has approved it for use as PrEP in adults at risk of HIV infection through sexual contact. There are several considerations to talk about with your health care provider to see if PrEP is the right choice for you. If you decide to take Truvada PrEP, your health care provider will prescribe it for you and monitor your health while you use it.

[Site: The text in the next two paragraphs applies to South American sites only. Sites should adjust the language in this paragraph to meet local PrEP availability.] Gilead Sciences, Inc. (the maker of Truvada) has agreed to provide Truvada as PrEP to study participants in HVTN 704/HPTN 085 through a local project. If you are interested, clinic staff can give you more information about this project and can refer you to it for PrEP.

PrEP has been shown to lower people's risk of getting HIV when taken once every day. There are several medical considerations to talk about with health care providers at the project to see if PrEP is the right choice for you. A provider at the project will prescribe PrEP for you and monitor your health while you use it.

In this study, we will look at how many participants use PrEP. We will also try to find out if using PrEP has any effect on how VRC01 works.

[Site: If you prefer to use Appendix E, Sample consent form for participants with HIV infection at enrollment or during the study, INCLUDE the following section and DELETE the two succeeding sections that are highlighted in green. If you prefer not to use Appendix E, DELETE the following section and INCLUDE the two sections highlighted in green.]

16. If you are HIV infected when you enroll or become infected during the study, we will help you get care and support.

We will test your blood for HIV before your first IV and during the study. Each time, it will take a few days to complete the tests. If you are infected with HIV, you cannot stay in the study for its whole length. If that happens, we will tell you as soon as possible. We will also ask you to come to the clinic for 3-6 more visits. We will tell you more about what will happen at these visits in another form.

17. If you are found to have been HIV-1 infected when you enrolled, or if you have HIV-2 infection:

If you are found to have been HIV infected when you enrolled, you were already infected with HIV before you got the antibody or placebo. It takes a few days to complete the tests to see if you have HIV, so your infection was not found until after you got your first IV.

HIV-2 is a rare kind of HIV, most often found in West Africa. In North and South America, there are only about a dozen cases reported each year.

We will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s).

We are asking you to come to the clinic for 1-2 more visits (including today) within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or side effects;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on how to avoid transmitting HIV to other people;
- Collect blood samples (between 30 and 45 mL, or about 2 to 3 tablespoons, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **second** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

18. If you got infected with HIV-1 during the study:

If you became infected with HIV-1, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). You will not get any more IVs. We will ask you to come in for 4-5 more visits within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or side effects;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;

- Collect blood samples (between 70 mL and 130 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **third** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

19. If you stop getting IVs for reasons other than HIV infection, we may encourage you to stay in the study.

In this case, we will ask you to come in for study visits about every 3-4 months until 104 weeks (2 years) after your first infusion. That is how long you would be in the study if you got all the infusions on schedule. Because you got some IVs, we want to keep track of your health. How many visits you will have will depend on when you stopped getting IVs. At these visits we will:

- Ask questions about your health, including medications you may be taking;
- Do physical exams based on your complaints or side effects;
- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Ask questions about any personal problems or benefits you may have from participating in the study;
- Do pregnancy tests if you could become pregnant; and
- Collect blood samples (between 70 mL and 120 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit).

*[Site: Insert the **last** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

20. We may stop your IVs and take you out of the study at any time. We may do this even if you want to stay in the study and even if you were scheduled for more IVs.

This may happen if:

- we learn that you were enrolled in the study in error,
- you are unable to follow instructions,
- we think that staying in the study might harm you,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

If we take you out of the study, we will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study.

21. We will stop your IVs if you become pregnant during the study.

We will encourage you to stay in the study if you choose. We will discuss your study options with you. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

22. We will do our best to protect your private information.

US sites: Check HIPAA authorization for conflicts with this section.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health, people who work for them, its study monitors, and its chosen South African representatives,
- The US Food and Drug Administration,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN and HPTN and people who work for them,
- The US National Institutes for Allergy and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.).

- [Item 1]

- [Item 2]
- [Item 3]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

Sites: The text below may not be deleted or changed, per FDA requirement. It's OK to remove the box around it.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Other Risks

23. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of taking blood:

Taking blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of the IV procedures:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in infections.

Personal problems/discrimination:

Some people who join HVTN or HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry,

get upset or angry, or assume that you are infected with HIV or at high risk and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

HIV testing

HIV antibody tests are the usual way to test for HIV infections. Although 2 out of 3 people in this study will get an HIV antibody, we do not expect them to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the VRC01 antibody and none of them detected the antibody.

Although it has not been seen so far, getting VRC01 may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

To be absolutely safe we ask you to get HIV tests only at this clinic during the study. Our tests can always detect true HIV infection. They can also tell if someone is really not HIV infected. Since the antibodies do not last long in the body, we do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you are infected with HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

Risks of genetic testing:

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

[*U.S. Sites, include the following paragraph*](#) In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the antibody will increase, decrease, or not change your risk of becoming infected with HIV if exposed.

If we find that you were already HIV infected when you got the antibody, we do not know how the antibody will affect your HIV disease. We also do not know how having gotten it will affect your HIV-related lab results.

If you get infected with HIV during the study, we do not know how the antibody might affect the course of your HIV disease.

If you become pregnant while you still have VRC01 in your body, we don't know if it could be passed to your baby. We do not know how the antibody will affect a pregnant participant or a developing baby.

Benefits

24. The study may not benefit you.

Since we do not know if the antibody can prevent HIV infection in people, you should not expect any benefit from getting the antibody in this study. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

This study may show us that the VRC01 antibody can prevent HIV and the study results may also help in the search for methods to prevent HIV. However, if the VRC01 antibody later becomes approved and sold or leads to an HIV prevention method, there are no plans to share any money with you.

Your rights and responsibilities

25. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

26. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

If you decide to leave the study, we will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Injuries

Sites: Do not make changes to the following section without obtaining approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org.

27. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, there is a process to decide if it is related to the VRC01 antibody and/or study procedures. If it is, we call it a study-related injury.

The HVTN and HPTN have limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

28. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies.

29. In Section 14 of this form, we told you about possible other uses of your extra samples and limited information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

30. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)

Participant's signature or mark

Date

Time

Clinic staff conducting consent discussion (print)

Clinic staff signature

Date

Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)

Witness's signature

Date

Time

*Witness is impartial and was present for the consent process.

Appendix B Approved birth control methods for transgender men (for sample informed consent form)

You should not become pregnant during the study because we do not know how the study antibody could affect the developing baby.

If you were assigned female at birth and are sexually active in a way that could lead to pregnancy, you must agree to use effective birth control from 21 days before your first IV until your last scheduled clinic visit (about 2 years after your first IV). You should not become pregnant during the study because we do not know how the antibody could affect the developing baby.

Although taking testosterone can lower the chances of becoming pregnant, it is not considered an effective method of birth control. Effective birth control means using any of the following methods every time you have sex:

- Drugs that are prescribed specifically for birth control and intended to prevent pregnancy—these include pills, shots, patches, vaginal rings, or inserts under the skin;
- Male or female condoms, with or without a cream or gel that kills sperm;
- Diaphragm or cervical cap with a cream or gel that kills sperm;
- Intrauterine device (IUD); or
- Any other contraceptive method approved by the researchers.

You do not have to use birth control if:

- You have had a hysterectomy (your uterus removed);
- You have had an oophorectomy (your ovaries removed); or
- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes; or
- You are sexually abstinent (no sex at all).

Remember: If you are having sex, you need to use male or female condoms to protect yourself from HIV infection.

If you join the study, we will test you for pregnancy at some visits, including before each study injection.

Appendix C Sample consent form for use of samples and information in other studies

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

HVTN protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in the United States.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

4. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

8. What information is shared with other researchers?

The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

U.S. Sites, include the following paragraph

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect

you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact [name and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact [name/title/phone of person on IRB or other appropriate organization].

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above and also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix D Tables of procedures (for sample informed consent form)

[Site: You may insert these tables of procedures into appropriate sections of your consent form(s) or give them to study volunteers/participants separately if you think they would be helpful. You are not required to do either.]

HIV-uninfected participants

	6 months														1 year					1½ years					2 years				
	Screening visit(s)	First IV visit	4 weeks	8 weeks	8 weeks + 5 days	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks	52 weeks	56 weeks	60 weeks	64 weeks	68 weeks	72 weeks	76 weeks	80 weeks	88 weeks	96 weeks	104 weeks			
Procedure																													
IV		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓								
Medical history	✓																												
Complete physical exam	✓																								✓				
Brief physical exam		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓								
Urine test	✓			✓																			✓						
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Pregnancy test*	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓		✓						
HIV test & pretest counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Risk reduction counseling	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓				✓				
Interview/Questionnaire	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓		✓		✓				
STI testing (blood, urine, and/or swabs) [†]		✓							✓						✓						✓								

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

[†] And if clinically indicated.

Participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Weeks after 1st positive HIV test	
	4	24
Medical history (as needed)	✓	✓
Brief physical (as needed)	✓	✓
Complete physical		✓
Risk reduction counseling	✓	✓
Questions/questionnaire	✓	✓
Blood drawn	✓	✓

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected

Procedure	Weeks after 1st positive HIV test				
	4	6	8	12	24
Medical history (as needed)	√	√	√	√	√
Brief physical (as needed)	√	√	√	√	
Complete physical					√
Risk reduction counseling	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√
Blood drawn	√	√	√	√	√
Pregnancy test*				√	

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected may be invited to join a separate study for follow-up visits. That study will have a separate schedule of visits and procedures. It will also have a separate consent form, which will be reviewed with all participants who are invited to join that study.

* Persons who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Participants who discontinue infusions for reasons other than HIV infection

Procedure	Weeks after enrollment							
	8	20	32	44	56	72	88	104
Brief physical (as needed)	√	√	√	√	√	√	√	
Complete physical								√
HIV testing & pretest counseling	√	√	√	√	√	√	√	√
Risk reduction counseling	√	√	√	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√	√	√	√
Urine test	√						√	
Pregnancy test*	√		√		√		√	
Blood drawn	√	√	√	√	√	√	√	√

Study participants who discontinue infusions for reasons other than HIV infection will start this visit schedule at the first visit that occurs after their last infusion. Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Appendix E Sample consent form for participants with HIV infection at enrollment or during the study

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

Protocol number: HVTN 704/HPTN 085, The AMP Study

Site: [Insert site name]

Please read this consent form or ask someone to read it to you. If you decide to, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

You are a participant in a study called HVTN 704/HPTN 085, The AMP Study. The rest of the information in the consent form that you signed earlier, about the study purpose, the risks and benefits of participation, your rights and responsibilities, and how your privacy is protected, continues to be important information for you and has not changed.

About this form

We tested your blood for HIV and you were found to be infected. We will help you get care and support.

You became infected either prior to enrollment or during your participation in the study. Because of this, you cannot stay in the study for its whole length. We would like you to come to the clinic for a different number of visits than what is explained in the main study consent form.

Depending on when you became infected, you will come to the clinic for 1-5 more visits, including today.

1. If you are found to have been HIV-1 infected when you enrolled, or if you have HIV-2 infection:

If you are found to have been HIV infected when you enrolled, you were already infected with HIV before you got the antibody or placebo. It takes a few days to complete the tests to see if you have HIV, so your infection was not found until after you got your first IV.

HIV-2 is a rare kind of HIV, most often found in West Africa. In North and South America, there are only about a dozen cases reported each year.

We will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s).

We are asking you to come to the clinic for 1-2 more visits (including today) within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;

- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 30 and 45 mL, or about 2 to 3 tablespoons, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

Site: You may remove the Table of procedures in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

Participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Weeks after 1 st positive HIV test	
	4	24
Medical history (as needed)	√	√
Brief physical (as needed)	√	√
Complete physical		√
Risk reduction counseling	√	√
Questions/questionnaire	√	√
Blood drawn	√	√

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

2. If you got infected with HIV-1 during the study:

If you became infected with HIV-1, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). You will not get any more IVs. We will ask you to come in for 4-5 more visits (including today) within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 70 mL and 130 mL, about 1/3 to 1/2 cup, at each visit); and

- Ask questions about any personal problems or benefits you may have from participating in the study.

Site: You may remove the Table of procedures (for addendum consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

HIV-1–infected participants

Procedure	Weeks after 1 st positive HIV test				
	4	6	8	12	24
Medical history (as needed)	√	√	√	√	√
Brief physical (as needed)	√	√	√	√	
Complete physical					√
Risk reduction counseling	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√
Blood drawn	√	√	√	√	√
Pregnancy test*				√	

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected may be invited to join a separate study for follow-up visits. That study will have a separate schedule of visits and procedures. It will also have a separate consent form, which will be reviewed with all participants who are invited to join that study.

* Persons assigned female at birth who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Leaving the study

Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Questions

If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

Your permissions and signature

If you agree to continue in this study with this new visit schedule, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand the changes to the visit schedule and what will happen to you. You understand that the possible risks and benefits of participation have not changed.
- You have had your questions answered and know that you can ask more at any time.
- You agree to continue in this study.

You will not be giving up any of your rights by signing this consent form.

_____	_____	_____	_____
Participant's name (print)	Participant's signature or mark	Date	Time
_____	_____	_____	_____
Study staff conducting consent discussion (print)	Study staff signature	Date	Time

For participants who are unable to read or write, also complete the signature block below:

_____	_____	_____	_____
Witness's name (print) [#]	Witness's signature	Date	Time

[#] Witness is impartial and was present for the consent process.

Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants

Procedure	Ship to ¹	Assay location ²	Tube Type ⁴	Tube size (vol. capacity) ⁴	Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total	
					Day:	Screening visit ³	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D616	D672	D728		
					Week:		W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W88	W96	W104		
						Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10								
BLOOD COLLECTION																																	
Screening/Diagnostic																																	
Screening HIV test																																	
	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5	
HIV diagnostics ⁷	UW-VSL / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20 ⁷	260	
Safety labs																																	
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	—	55
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	—	55
STI Serology																																	
Syphilis ¹¹	Local lab	Local lab	SST	5mL	—	5 ¹³	—	—	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	20	
Drug Levels/Detection																																	
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
ARV detection by serum or plasma ^{8, 10}	CSR	JHU	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
ARV detection by dried blood spots ¹⁰	CSR	HVTN Labs	EDTA	2mL	—	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	50
Immunogenicity & Virologic Assays																																	
Host genetics ⁵	CSR	HVTN Labs	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0	
Anti-VRC01 Ab levels	CSR	VRC / NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	y	—	—	—	—	—	—	—	—	—	—	y	—	—	—	—	0	
Functional humoral assays ⁸	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
Viral isolation/sequencing ⁹	CSR	TBD	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	250	
STORAGE																																	
Serum storage	CSR	—	SST	8.5mL	—	76.5	51	51	42.5	51	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	1139	
PBMC storage	CSR	—	ACD	8.5mL	—	51	—	—	—	—	—	—	—	—	—	—	34	—	—	—	—	—	—	—	—	34	—	—	—	—	—	153	
Visit total ¹⁶					15	168	76	86	68	76	78	68	83	68	78	76	112	68	83	68	78	68	78	68	117	76	68	68	68	112	2062		
56-Day total					15	183	259	345	230	306	307	221	228	218	228	221	265	255	262	218	228	213	223	213	262	260	260	135	135	179			
URINE COLLECTION																																	
Urine dipstick ¹⁵	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—		
Pregnancy Test ⁶	Local lab	Local lab			X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—		
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	—	X ¹³	—	—	—	—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—		
RECTAL SWAB COLLECTION																																	
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—		
OROPHARYNGEAL SWAB COLLECTION																																	
Gonorrhea ¹²	Local lab	Local lab			—	X ¹⁴	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: Cape Town HVTN Immunology Laboratory (CHIL, Cape Town, South Africa); South African Immunology Laboratory—National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa); University of Colorado Denver (Aurora, Colorado, USA). Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

TBD = Laboratories to be determined by HVTN Laboratory Program.

³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

⁴ Local labs may assign appropriate alternative tube types for locally performed tests.

⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

⁶ For persons capable of becoming pregnant, pregnancy test must be performed on urine or blood specimens on the day of infusion with negative results received prior to infusion.

⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.

⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

¹⁰ Testing plan for ARV detection to be determined.

¹¹ Syphilis testing will be done by serology.

¹² Nucleic acid amplification testing (NAAT) for chlamydia and gonorrhea will be performed on urine and on rectal and oropharyngeal swabs.

¹³ Syphilis testing, and chlamydia/gonorrhea testing by urine and rectal swab, will be performed at visits 2, 9, 15 and 21; in addition, testing may occur at any visit if clinically indicated.

¹⁴ Gonorrhea testing by oropharyngeal swab will be performed at visit 2; in addition, testing may occur at any visit if clinically indicated. A combination gonorrhea/chlamydia oropharyngeal test is allowable (see the SSP for results reporting).

¹⁵ And microscopy if needed.

¹⁶ A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. This is not applicable to the screening visit. Refer to the Specimen Collection SSP for more information.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants

						Visit: #X ⁵	Visit: 31 Days: D28	32 D42	33 D56	34 D84	35 D168	
							Weeks after diagnosis ⁷ : W4	W6	W8	W12	W24	
Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³								Total
BLOOD COLLECTION												
Screening or diagnostic assays												
HIV diagnostics	UW-VSL / Peru CTU Laboratory/ CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory/ CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	20	—	—	—	—	—	—	20
HIV PCR viral load	UW-VSL / Peru CTU Laboratory/ CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory/ CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—	10	10	10	10	10	10	50
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5	5	5	5	5	5	5	30
Safety lab												
Hemoglobin	Local Lab	Local Lab	EDTA	5mL	—	—	—	5	5	—	—	10
Drug levels												
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5	8.5	8.5	8.5	8.5	8.5	8.5	51
Immunogenicity & Virologic Assays												
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17	17	17	17	17	17	17	102
Viral isolation/sequencing	CSR	TBD	EDTA	10mL	10	10	10	10	10	10	10	60
Storage												
Serum	CSR		SST	8.5mL	25.5	17	17	17	17	17	17	110.5
Plasma	CSR		EDTA	5mL	5	5	5	5	5	5	5	30
PBMC	CSR		ACD	8.5mL	34	—	—	—	34	34	34	102
Visit total ⁸					128	75.5	75.5	80.5	114.5	109.5	584	
56-Day total					128	204	279	360	346	109.5		
URINE COLLECTION												
Pregnancy Test ⁴	Local Lab	Local Lab			X	—	—	—	X	—	—	

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology, Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA)

TBD = Laboratories to be determined by HVTN Laboratory Program.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

⁸ A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. Refer to the Specimen Collection SSP for more information.

Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

						Visit: #X ⁵	Visit: Days:	47 D28	48 D168	Total
							Weeks after diagnosis ⁷ :	W4	W24	
Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³						
BLOOD COLLECTION										
Screening or diagnostic assays										
HIV diagnostics	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	20		—	—	—	20
HIV PCR viral load	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	—		10	10	10	20
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5		5	5	5	15
Drug levels										
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5		—	—	—	8.5
Immunogenicity & Virologic Assays										
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17		—	—	—	17
Viral isolation/sequencing	CSR	TBD	EDTA	10mL	10		—	—	—	10
Storage										
Serum	CSR		SST	8.5mL	25.5		17	17	17	59.5
Plasma	CSR		EDTA	5mL	5		—	—	—	5
PBMC	CSR		ACD	8.5mL	34		—	—	—	34
Visit total⁸					128		35	35	35	198
56-Day total					128		163	35	35	
URINE COLLECTION										
Pregnancy Test ⁴	Local Lab	Local Lab			X		—	—	—	

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA).

TBD = Laboratories to be determined by HVTN Laboratory Program.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For persons capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

⁸ A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. Refer to the Specimen Collection SSP for more information.

Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection

Procedure	Ship to ¹	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³	Visit:	71	72	73	74	75	76	77	78	Total
					Days after enrollment:	D56	D140	D224	D308	D392	D504	D616	D728	
					Weeks after enrollment:	W8	W20	W32	W44	W56	W72	W88	W104	
BLOOD COLLECTION														
Screening or diagnostic assays														
HIV diagnostics ⁵	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	UW-VSL / Peru CTU Laboratory / CADIG-Immunodiagnostic Lab (INI-FIOCRUZ)	EDTA	10mL	10	10	10	10	10	10	10	10	20 ⁵	90
Safety labs														
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	—	5	—	5	—	—	—	—	15
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	—	5	—	5	—	—	—	—	15
Drug Levels/Detection														
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	y	0
ARV detection by serum or plasma ⁸	CSR	JHU	SST	8.5mL	y	y	y	y	y	y	y	y	y	0
ARV detection by dried blood spots ⁸	CSR	HVTN Labs	EDTA	2mL	2	2	2	2	2	2	2	2	2	16
Immunogenicity & Virologic Assays														
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	y	0
Viral isolation/sequencing ⁸	CSR	TBD	EDTA	10mL	10	10	10	10	10	10	10	10	10	80
STORAGE														
Serum storage	CSR	—	SST	8.5mL	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	349
PBMC storage	CSR	—	ACD	8.5mL	—	—	—	—	—	—	—	—	34	34
Visit total ¹⁰						86	68	78	68	78	68	68	112	623
56-Day total						86	68	78	68	78	68	68	112	
URINE COLLECTION														
Urine dipstick ⁷	Local lab	Local lab			X	—	—	—	—	—	—	X	—	
Pregnancy Test ⁴	Local lab	Local lab			X	—	X	—	X	—	—	X	—	

¹ CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Peru CTU Laboratory (Lima, Peru); CADIG - Immunodiagnostic Lab (INI-FIOCRUZ) (Rio de Janeiro, Brazil).

² HVTN Laboratories include: South African Immunology Laboratory—National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Colorado Denver (Denver, Colorado, USA).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

TBD = Laboratories to be determined by HVTN Laboratory Program.

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ For participants capable of becoming pregnant; pregnancy test may be performed on urine or blood specimens.

⁵ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 78 above.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ And microscopy if needed.

⁸ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.

⁹ Testing plan for ARV detection to be determined.

¹⁰ A 3mL volume is included in the visit totals for drawing a non-additive discard tube to prevent blood tube additive cross-contamination. Refer to the Specimen Collection SSP for more information.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level and functional humoral assays; no separate blood draw is needed.

Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants

Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Post
Day:	Screening	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D616	D672	D728	
Week:	visit ¹	W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W88	W96	W104	
Procedure	Scr.	Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10						
Study procedures²																											
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Risk reduction counseling	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Pregnancy prevention assessment ³	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Participant Questionnaire	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Concomitant medications	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
Intercurrent illness/adverse experience	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	X	—
HIV infection assessment ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant ¹²	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Local lab assessment																											
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine dipstick ¹¹	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Pregnancy (urine or serum HCG) ⁵	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
CBC, differential	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
ALT, Creatinine	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Syphilis ⁶	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—
Chlamydia, Gonorrhea ⁸	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—
Study product administration procedures																											
IV infusion ⁹	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Reactogenicity assessment ¹⁰	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
Poststudy																											
Unblind participant	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

² For specimen collection requirements, see Appendix F.

³ Pregnancy prevention assessments are required only for participants who are capable of becoming pregnant.

⁴ Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

⁵ For a participant capable of becoming pregnant, pregnancy test must be performed on the day of infusion prior to infusion. Pregnancy test to determine eligibility may be performed at screening, but must also be done on Day 0 prior to infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.

⁶ Syphilis testing will be done by serology.

⁷ Syphilis and Chlamydia/Gonorrhea testing will be performed at visits 2, 9, 15, and 21; in addition, testing may occur at any visit or if clinically indicated.

⁸ Chlamydia/Gonorrhea testing will be done with urine and rectal swabs; oropharyngeal swabs will be collected for gonorrhea testing at visit 2; in addition, testing may occur at any visit if clinically indicated. A combination gonorrhea/chlamydia oropharyngeal test is allowable (see the SSP for results reporting).

⁹ Blood draws required at infusion visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests must be drawn within the 3 days prior to infusion.

¹⁰ Reactogenicity assessments performed for 3 days postinfusion (see Section 7.10).

¹¹ And microscopy if needed.

¹² If HIV test results are not available at the visit indicated, provide test results at next available opportunity.

Appendix K Schedule 2—Procedures at CRS for HIV-1–infected participants

Visit Number:	#.X ¹		31	32	33	34	35
		Days after diagnosis ²	D28	D42	D56	D84	D168
		Weeks after diagnosis	4	6	8	12	24
Study procedures³							
Counseling on HIV-1 testing/diagnosis	X		X	—	—	—	—
Abbreviated physical exam ⁴	X		X	X	X	X	—
Complete physical exam ⁴	—		—	—	—	—	X
ART assessment	X		X	X	X	X	X
Concomitant medications	—		X	X	X	X	X
Intercurrent illness/adverse experience	—		X	X	X	X	X
Transmission risk reduction counseling	X		X	X	X	X	X
Behavioral risk assessment questionnaire	—		—	—	—	—	X
Social impact assessment	X		X	X	X	X	X
Local lab assessment³							
Pregnancy test ⁵	X		—	—	—	X	—
CD4+ T cell count	X		X	X	X	X	X
Hemoglobin					X	X	

¹ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple Redraw visits may be necessary; only the blood specimen indicated in Appendix G will be collected at the subsequent Redraw visits.

² Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request

³ For specimen collection requirements, see Appendix G.

⁴ Includes assessment of HIV/AIDS-related conditions.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix L Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Visit Number	#.X ¹		47	48
		Days after diagnosis ²	D28	D168
		Weeks after diagnosis	4	24
Study procedures³				
Counseling on HIV-1 testing/diagnosis	X		X	—
Abbreviated physical exam ⁴	X		X	—
Complete physical exam ⁴	—		—	X
ART assessment	X		X	X
Concomitant medications	—		X	X
Intercurrent illness/adverse experience	—		X	X
Transmission risk reduction counseling	X		X	X
Behavioral risk assessment questionnaire	—		—	X
Social impact assessment	X		X	X
Local lab assessment³				
Pregnancy test ⁵	X		—	—
CD4+ T cell count	X		X	X

¹ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple Redraw visits may be necessary; only the blood specimens indicated in Appendix H will be collected at the subsequent Redraw visits.

² Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request

³ For specimen collection requirements, see Appendix H.

⁴ Includes assessment of HIV/AIDS-related conditions.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection

Visit Number:	71	72	73	74	75	76	77	78
Days after enrollment:	56	140	224	308	392	504	616	728
Weeks after enrollment:	8	20	32	44	56	72	88	104
Study procedures¹								
Abbreviated physical exam	X	X	X	X	X	X	X	—
Complete physical exam	—	—	—	—	—	—	—	X
Risk reduction counseling	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X
Intercurrent illness/adverse experience	X	X	X	X	X	X	X	X
HIV infection assessment ²	X	X	X	X	X	X	X	X
Confirm HIV test results provided to participant ³	X	X	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	X	—	X	—	X	—	X
Social impact assessment	X	X	X	X	X	X	X	X
Local lab assessment¹								
Urine dipstick ⁴	X	—	—	—	—	—	X	—
Pregnancy test ⁵	X	—	X	—	X	—	X	—

¹ For specimen collection requirements, see Appendix I.

² Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

³ If HIV test results are not available at the visit indicated, provide test results at next available opportunity.

⁴ And microscopy if needed.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix N Protocol Signature Page

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)

Investigator of Record Signature

Date

DAIDS Protocol Number: HVTN 704/HPTN 085

DAIDS Protocol Version: Version 3.0

Protocol Date: June 15, 2017

Protocol modification history

Protocol modifications are made to HVTN protocols via clarification memos, letters of amendment, or full protocol amendments. HVTN protocols are modified and distributed according to the standard HVTN procedures as described in the HVTN Manual of Operations (MOP).

The version history of, and modifications to, Protocol HVTN 704/HPTN 085 are described below.

Date: April 2, 2020

Protocol version: Version 3.0

Protocol modification: Clarification Memo 2

- Item 1 Clarified throughout protocol: “Clinic visits”
- Item 2 Clarified in Section 1, *Overview* and Section 6, *Study product preparation and administration*: Study product administration halted

Date: October 4, 2018

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 4

- Item 1 Updated in Section 6.3 and 6.4: Storage conditions for prepared IV bags and IV glass bottles
- Item 2 Updated in Sections 10 and 15: URLs for accessing DAIDS AE reporting documents

Date: June 18, 2018

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 3

- Item 1 Updated in Sections 6.3 and 6.4: Storage conditions for prepared IV bags
- Item 2 Updated in Section 1.1, *Protocol Team*: Co-chair institutional affiliation and Consultative investigators
- Item 3 Clarified in Sections 2.4.4 and 5.3.3: Reactive HIV tests and discontinuation of infusions
- Item 4 Revised and corrected in Section 1, *Overview* and Appendices F through I: Endpoint lab listings

Date: March 7, 2018

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 2

- Item 1 Corrected in Sections 6.3.1 and 6.3.3: IV bag/glass bottle labeling instructions

- Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

Date: November 9, 2017

Protocol version: Version 3.0

Protocol modification: Clarification Memo 1

- Item 1 Clarified in Section 6, *Study product preparation and administration*: Sodium Chloride for Injection USP, 0.9% containers and volumes

Date: August 29, 2017

Protocol version: Version 3.0

Protocol modification: Letter of Amendment 1

- Item 1 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/handling instructions
- Item 2 Revised in Section 4.9.3, *Monitoring for futility to assess PE*: Futility to assess PE monitoring targets
- Item 3 Clarified in Section 5, *Selection and withdrawal of participants*: Eligibility determination
- Item 4 Updated: Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events
- Item 5 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedures at week 80 for HIV-uninfected participants
- Item 6 Clarified in Appendices F through I: Assay locations, discard tubes not required, and blood draw totals
- Item 7 Added in Appendix M, *Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection*: Participant unblinding
- Item 8 Added in Appendix J and M: Post-study confirmation of final HIV test results

Date: June 15, 2017

Protocol version: Version 3.0

Protocol modification: Full Protocol Amendment 2

- Item 1 Revised: Study duration and participant follow-up
- Item 2 Updated in Section 1.1: Protocol team membership
- Item 3 Updated in Sections 2.9, 2.9.3, 2.9.4, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 4 Revised in Section 4.9.3: *Monitoring for futility to assess PE*
- Item 5 Clarified in Section 5.1, *Inclusion criteria*: Transgender volunteer eligibility

- Item 6 Added in Section 5.1, *Inclusion criteria*: Hgb criterion adjustment for MTF transgender volunteers using feminizing hormones
- Item 7 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 8 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature
- Item 9 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation
- Item 10 Updated in Section 6.4 and Appendix A: Minimum infusion time
- Item 11 Added in Section 6.4, *Administration*: In-line filter set requirement
- Item 12 Clarified in Section 6.4, *Administration*: IV bag temperature equilibration and label weight
- Item 13 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 14 Updated in Section 7.10, *Assessments of reactogenicity*, and Section 10.2.2, *AE reporting*: DAIDS AE grading table version and exceptions
- Item 15 Updated in Section 10.2, *Safety reporting*: URLs for referenced documents
- Item 16 Clarified in Section 10.2.2, *AE reporting*: Working hours for CSS or RML response
- Item 17 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*
- Item 18 Updated in Section 14: Version history
- Item 19 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 20 Corrected in Section 16: *Acronyms and abbreviations*
- Item 21 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 22 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 23 Added in Appendix B, *Approved birth control methods for transgender men (for sample informed consent form)*: Condom use and pregnancy testing
- Item 24 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoints
- Item 25 Updated in Appendices F through I: Assay locations, HVTN laboratory listings, and blood draw totals
- Item 26 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X
- Item 27 Removed in Appendices G and H: Footnote regarding whole blood for HIV diagnostics
- Item 28 Clarified in Appendices J and M: Provision of HIV test results

Item 29 Added as Appendix N: Protocol signature page

Item 30 Revised in Letter of Amendment 1 to Version 2.0: Interim safety and feasibility assessments

Item 31 Corrected: Minor typographical, grammatical, and formatting errors

Date: December 14, 2016

Protocol version: Version 2.0

Protocol modification: Letter of Amendment 1

Item 1 Revised in Section 1, *Overview* and Section 4.9.1, *Role of the Data Safety Monitoring Board (DSMB)*: Interim safety assessments

Item 2 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment

Date: July 19, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

Item 1 Corrected in Section 1, *Overview*: Estimated total study duration

Item 2 Added: Switzerland as study location

Item 3 Added in Section 1 and Appendices F through I: HIV diagnostic laboratories in Peru and Brazil

Item 4 Updated in Section 1.1: *Protocol team* membership

Item 5 Revised: PrEP monitoring

Item 6 Removed in Section 2.9.3, *HVTN 104*: Incorrect systemic reactogenicity rate

Item 7 Clarified in Sections 4.9.1 and 10.4.3: Data reporting to DSMB

Item 8 Clarified in Section 4.9.1.1, *Sequential monitoring for potential harm, non-efficacy, and high efficacy*: Caption to Figure 4-6

Item 9 Added in Section 5.1, *Inclusion criteria*: Reference to SSP for clarification of transgender eligibility

Item 10 Clarified in Section 5.2, *Exclusion criteria*: PSRT may permit exceptions to Exclusion criterion #4

Item 11 Clarified in Section 6, *Study product preparation and administration*: Administration volumes, bag covers, and expiration prompts

Item 12 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications

Item 13 Clarified in Section 7.3, *Enrollment and infusion visits* and Section 7.10, *Assessment of reactogenicity*: Recording and source documentation for reactogenicity events

Item 14 Clarified in Section 7.3, *Enrollment and infusion visits*, and Appendices D, F, and J: STI testing

- Item 15 Clarified in Section 7.9, *Urine testing*: Follow-up to abnormal urine dipstick result at screening
- Item 16 Clarified in Appendix A, *Sample informed consent form*: VRC01 not being developed for sale
- Item 17 Added in Appendix A, *Sample informed consent form*: Option to include consent for HIV-infected study participants
- Item 18 Renumbered in Appendix A: Section 19, “If you stop getting IVs for reasons other than HIV infection...”
- Item 19 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 20 Clarified in Appendix E, *Sample consent form for participants with HIV infection at enrollment or during the study*: Number of visits, physical exams, and HIV transmission risk counseling
- Item 21 Throughout protocol document: Minor errors corrected
- Item 22 Updated: Section 14, *Version history*

Date: March 9, 2016

Protocol version: Version 1.0

Protocol modification: Original protocol



PROTOCOL

HVTN 703/HPTN 081

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

DAIDS DOCUMENT ID 12045

IND 113,611 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS
Bethesda, Maryland, USA

August 11, 2015

HVTN 703/HPTN 081, Version 1.0

Contents

1	Overview	5
1.1	Protocol Team.....	8
2	Background	10
2.1	Rationale for trial concept	10
2.2	bNabs to HIV-1	11
2.3	VRC01: VRC-HIVMAB060-00-AB	14
2.4	Trial design rationale	15
2.5	Combination Prevention for HIV acquisition.....	21
2.6	Plans for future product development and testing	22
2.7	Preclinical safety studies.....	23
2.8	Nonhuman primate (NHP) studies of VRC01	26
2.9	Phase 1 clinical trial experience	28
2.10	Potential risks of study products and administration	33
3	Objectives and endpoints	35
3.1	Primary objectives and endpoints.....	35
3.2	Secondary objectives and endpoints	35
3.3	Exploratory objectives.....	36
4	Statistical considerations.....	37
4.1	Outline of the statistical considerations section.....	37
4.2	PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests.....	37
4.3	Statistical rationale for the 3-arm design compared to a 2-arm design.....	38
4.4	Sample size calculations for testing for overall PE (Primary objective 2) ..	39
4.5	Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group	50
4.6	Sample size calculations for safety	51
4.7	Monitoring of the trial	53
4.8	Assessment of ARV drug use	57
4.9	Randomization.....	58
4.10	Blinding	58
4.11	Statistical analyses	59
5	Selection and withdrawal of participants	69
5.1	Inclusion criteria	69
5.2	Exclusion criteria	71
5.3	Participant departure from infusion schedule or withdrawal	72
6	Study product preparation and administration	75
6.1	Study product regimen.....	75
6.2	Study product formulation.....	76
6.3	Preparation of study products	76
6.4	Administration	78
6.5	Acquisition of study products.....	78
6.6	Pharmacy records.....	78
6.7	Final disposition of study products.....	78
7	Clinical procedures	79
7.1	Informed consent	79
7.2	Pre-enrollment procedures.....	81

7.3	Enrollment and infusion visits	82
7.4	Follow-up visits	84
7.5	HIV counseling and testing	84
7.6	Contraception status.....	85
7.7	Urine testing	86
7.8	Assessments of reactogenicity	86
7.9	Visit windows and missed visits.....	87
7.10	Early termination visit	87
7.11	Pregnancy	87
8	HIV infection assessment and clinical response	88
8.1	HIV symptom assessment.....	88
8.2	HIV screening test (prior to randomization).....	88
8.3	HIV testing postinfusion.....	88
8.4	Endpoint adjudication.....	89
8.5	HIV infection during the study	89
8.6	Medical care for participants who become HIV infected	90
9	Laboratory.....	91
9.1	CRS laboratory procedures.....	91
9.2	Total blood volume.....	91
9.3	Assay timepoints.....	91
9.4	VRC01 mAb levels.....	91
9.5	Endpoint assays: humoral	92
9.6	ARV detection	92
9.7	Host (human) genotyping	93
9.8	Lab assay algorithm.....	93
9.9	Possible additional studies.....	93
9.10	Other use of stored specimens	93
9.11	Biohazard containment	94
10	Safety monitoring and safety review	95
10.1	Safety monitoring and oversight.....	95
10.2	Safety reporting	96
10.3	Safety pause and prompt PSRT AE review	98
10.4	Review of cumulative safety data.....	100
10.5	Study termination.....	100
10.6	Social impact reporting.....	100
11	Protocol conduct	102
11.1	Emergency communication with study participants	103
12	Ethical considerations	104
13	IRB/EC/RE review considerations.....	106
13.1	Minimized risks to participants	106
13.2	Reasonable risk/benefit balance	107
13.3	Equitable subject selection	107
13.4	Appropriate informed consent	107
13.5	Adequate safety monitoring.....	107
13.6	Protect privacy/confidentiality.....	108
14	Version history.....	109
15	Document references (other than literature citations).....	110
16	Acronyms and abbreviations.....	112

17	Literature cited.....	116
	Appendix A Sample informed consent form.....	129
	Appendix B Approved birth control methods for African women (for sample informed consent form)	146
	Appendix C Approved birth control methods for transgender men in the Americas (for sample informed consent form)	147
	Appendix D Sample consent form for use of samples and information in other studies	148
	Appendix E Table of procedures (for sample informed consent form)	152
	Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants	153
	Appendix G Schedule 2—Laboratory procedures for HIV-infected participants	154
	Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV infected at enrollment	155
	Appendix I Schedule 1—Procedures at CRS for HIV-uninfected participants	156
	Appendix J Schedule 2—Procedures at HVTN CRS for HIV-infected participants	158
	Appendix K Schedule 3—Procedures at HVTN CRS for participants discovered to have been HIV infected at enrollment.....	159

1 Overview

Title

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

Primary objectives

- To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in each of 2 cohorts
- To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in each of 2 cohorts

Study products and routes of administration

- VRC01:** human monoclonal antibody (mAb) VRC-HIVMAB060-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered at a final volume of 150 mL intravenously (IV)
- Control for VRC01:** Sodium Chloride for Injection 0.9%, USP administered at a volume of 150 mL IV

Table 1-1 Schema

				Infusion schedule (Weeks)											
				[A = VRC01 infusion; C = Control infusion]											
	Cohort	Treatment	N	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80*	W92†
Group 1	North + South American MSM & TG	VRC01 10 mg/kg	800	A	A	A	A	A	A	A	A	A	A		
Group 2		VRC01 30 mg/kg	800	A	A	A	A	A	A	A	A	A	A		
Group 3		Control	800	C	C	C	C	C	C	C	C	C	C		
Group 4	sub-Saharan African women	VRC01 10 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 5		VRC01 30 mg/kg	500	A	A	A	A	A	A	A	A	A	A		
Group 6		Control	500	C	C	C	C	C	C	C	C	C	C		
	Total	3900 (1300 VRC01 30 mg/kg; 1300 VRC01 10 mg/kg; 1300 control)													

MSM = men who have sex with men. TG = male-to-female and female-to-male transgender persons.

* Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.

† Week 92 occurs at 20 weeks after the final infusion. It is the last study visit for the co-primary endpoint analysis of safety and tolerability.

Participants

3900 HIV-1–uninfected volunteers aged 18 to 50 years; in North and South America, 2400 men who have sex with men (MSM) or with transgender persons (TG) and TG who have sex with men or TG; in sub-Saharan Africa, 1500 women at risk of HIV-1 infection; 2:1 active:control allocation within each cohort; total 2600 VRC01 mAb, 1300 control

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

21 months of scheduled clinic visits

Estimated total study duration

57 months (includes enrollment and follow-up, including follow-up for HIV-infected participants)

Investigational New Drug (IND) sponsor

DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Study product providers

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (FHCRC) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC), FHI360 (Durham, North Carolina, USA)

Statistical and data management center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), FHCRC (Seattle, Washington, USA)

DF/Net Research (Seattle, Washington, USA)

Endpoint assay laboratories

- University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)
- Duke University Medical Center (Durham, North Carolina, USA)
- FHCRC/University of Washington (Seattle, Washington, USA)

- South Africa Immunology Laboratory, National Institute for Communicable Diseases (SAIL-NICD) (Johannesburg, South Africa)
- HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (HSML-NICD) (Johannesburg, South Africa)
- NIAID Vaccine Immune T-Cell Antibody Laboratory (NVITAL) (Gaithersburg, Maryland, USA)
- HPTN Laboratory Center (LC), Johns Hopkins University (Baltimore, Maryland, USA)

Study sites

Clinical Research Sites (CRSs) to be specified in the Site Announcement Memo

Safety monitoring

HVTN 703/HPTN 081 Protocol Safety Review Team (PSRT); NIAID Data and Safety Monitoring Board (DSMB)

1.1 Protocol Team

Protocol leadership

<i>Chair</i>	Lawrence Corey HVTN; FHCRC 206-667-6770 lcorey@fhcrc.org	<i>Statistician</i>	Allan DeCamp SCHARP, FHCRC 206-667-7892 adecamp@scharp.org
<i>Chair</i>	Myron Cohen HPTN; University of North Carolina 919-966-2536 mscohen@med.unc.edu	<i>Statistician</i>	Deborah Donnell SCHARP, FHCRC 206-667-5661 deborah@scharp.org
<i>Cochair</i>	Srilatha Edupuganti Emory University 404-712-1434 sedupug@emory.edu	<i>Medical officer</i>	Margarita Gomez Lorenzo Vaccine Research Program (VRP), DAIDS, NIAID 240-627-3510 gomezmm@niaid.nih.gov
<i>Cochair</i>	Nyaradzo Mgodzi UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe 263-4-704890 nmmgodzi@uz- ucsf.co.zw	<i>Medical officer</i>	David Burns Prevention Sciences Program (PSP), DAIDS, NIAID 301-435-8896 burnsda@niaid.nih.gov
<i>Protocol Team leader</i>	Shelly Karuna HVTN Core, FHCRC 206-667-4355 skaruna@hvtn.org	<i>HVTN Laboratory lead</i>	John Hural HVTN Laboratory Program 206-667-1683 jhural@hvtn.org

Other contributors to the original protocol

<i>HVTN Core medical monitor</i>	Shelly Karuna HVTN Core, FHCRC	<i>DAIDS protocol pharmacist</i>	Scharla Estep DAIDS, NIAID 240-627-3046
<i>HVTN regional medical liaison, Southern Africa</i>	Simba Takuva HVTN Core, FHCRC	<i>Statisticians</i>	Peter Gilbert SCHARP, FHCRC
<i>HVTN Clinical safety specialist</i>	Maija Anderson HVTN Core, FHCRC		Michal Juraska SCHARP, FHCRC
<i>HVTN/HPTN investigator</i>	Ken Mayer Fenway Health	<i>HVTN Statistical research associate</i>	Nidhi Kochar SCHARP, FHCRC
	LaRon Nelson Univ. of Rochester CRS	<i>HVTN Social behavioral scientist</i>	Michele Andrasik HVTN Core, FHCRC
	Manuel Villarán IMPACTA, Lima, Peru	<i>HPTN LOC director</i>	Nirupama Sista HPTN LOC, FHI360
<i>Product developer representatives</i>	John Mascola VRC	<i>HPTN Clinical research managers</i>	Philip Andrew HPTN LOC, FHI360

	Barney Graham VRC		Elizabeth Greene HPTN LOC, FHI360
	Julie Ledgerwood VRC	<i>HVTN Clinical trials manager</i>	Carissa Karg HVTN Core, FHCRC
<i>HVTN Laboratory Program representatives</i>	On Ho HVTN Laboratory Program, FHCRC	<i>HPTN SDMC Associate director</i>	Lynda Emel SCHARP, FHCRC
	David Montefiori HVTN Laboratory Program, Duke Univ.	<i>HVTN SDMC program manager</i>	Gina Escamilla SCHARP, FHCRC
<i>HPTN Laboratory Center representatives</i>	Susan Eshleman HPTN LC, Johns Hopkins Univ.	<i>SDMC project manager</i>	Lisa Sunner SCHARP, NIAID
	Vanessa Cummings HPTN LC, Johns Hopkins Univ.	<i>HVTN Protocol development manager</i>	Carter Bentley HVTN Core, FHCRC
	Estelle Piwowar- Manning HPTN Laboratory Center, Johns Hopkins Univ.	<i>HVTN Communications unit representative</i>	Jim Maynard HVTN Core, FHCRC
<i>HVTN Regulatory affairs</i>	Megan Brandon HVTN Core, FHCRC	<i>HVTN Community engagement unit representative</i>	Gail Broder HVTN Core, FHCRC
<i>Clinic coordinators</i>	Debora Dunbar Philadelphia CRS	<i>HPTN Community program associates</i>	Jonathan Lucas HPTN LOC, FHI360
	Lilian Saavedra Asociación Civil Selva Amazónica, Iquitos, Peru		Jontraye Davis HPTN LOC, FHI360
	Elaine Sebastian Desmond Tutu HIV Centre, University of Cape Town	<i>Community educator/recruiters</i>	DaShawn Usher New York Blood Center CRS
<i>Community Advisory Board (CAB) members</i>	Mark Hubbard Nashville CAB		Luciana Kamel Instituto de Pesquisa Clinica Evandro Chagas (IPEC) CRS
	Likhapha Faku HVTN Global CAB	<i>HVTN Technical editor</i>	Erik Schwab HVTN Core, FHCRC
	Jim Wick San Francisco CAB		

2 Background

2.1 Rationale for trial concept

Effective biomedical interventions are needed to reduce the acquisition of HIV. The global HIV-1 epidemic continues and while many countries have made progress toward leveling HIV prevalence over the last few years, micro-epidemics of infection continue to occur in nearly all regions, even in countries possessing the full toolkit of proven prevention approaches [1-4].

Antiretroviral drugs (ARVs) have been shown to be effective for HIV prevention in serodiscordant couples when administered to HIV-infected individuals as treatment as prevention (TasP) and clinical trials are now underway to evaluate the efficacy of TasP at a population level [5]. ARVs have also been shown to be effective as pre- or post-exposure prophylaxis (PrEP or PEP) [6]. At present daily oral emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Truvada) is the only drug approved for PrEP use, but this drug combination has significant known side effects [7]. The requirement for daily use and the side effect profile have made adherence to this drug regimen challenging, especially over long periods of time [8]. As a consequence, the capacity of currently available ARV regimens to reduce HIV incidence or prevalence is less than optimal. Furthermore, sustained use of ARVs for HIV prevention will increase the already significant burden of ARV manufacturing and delivery for HIV treatment. For these reasons, a biomedical HIV prevention approach that exhibits sustained activity over an extended time period, that has a safety profile acceptable for healthy persons, and whose effectiveness is less dependent upon individual adherence, is still needed. In this vein, two long-acting injectable ARVs (TMC278 and GSK744) are under consideration as PrEP agents. These are currently in early phase testing for safety, tolerability, and acceptability (eg, HPTN 076 and HPTN 077).

An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies, a strategy that has been employed for more than 100 years against diverse disease targets and that is still used for hepatitis A and B prophylaxis [9,10] and for PEP for rabies, measles, varicella zoster, and other infectious diseases [11]. Most notably, palivizumab has been used for respiratory syncytial virus (RSV) prophylaxis in pre-term and other high-risk infants for nearly two decades. In 1998, a multinational, randomized controlled trial showed that palivizumab administered during the RSV season reduce RSV-associated hospitalizations by 39–78% in premature infants and in children with bronchopulmonary dysplasia [12]. Subsequent studies have confirmed palivizumab's safety, efficacy, and clinical benefit for infants at high risk for RSV infection [13,14]. Hence, palivizumab serves as a model for the use of mAbs to block a mucosally-acquired infection. Significantly, passive administration of this antibody has also set a standard by which candidate RSV vaccines are evaluated, by defining antibody levels that effectively inhibit fusion by RSV. This precedent has informed the conceptual framework for this study.

Over the past several years, there has been a concerted and notably successful effort to isolate broadly neutralizing antibodies (bNab) to HIV-1 from chronically infected donors [15-31]. Subsequent research has provided considerable insight into the sites these antibodies target on HIV-1 and their functionality (ie, the mechanisms by which they

neutralize the virus) [18,19,28,32]. This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies [33-36], prompting optimism that vaccines that elicit bNabs against HIV-1 can be developed [34,37]. In addition, the availability of bNabs against HIV opens the exciting possibility of antibody-mediated prevention (AMP) of HIV infection.

The Vaccine Research Center (VRC), NIAID, NIH has developed VRC01, a broadly neutralizing human mAb that targets the HIV-1 CD4 binding site [17]. This mAb was originally discovered in a participant infected with HIV-1 for more than 15 years who maintained viral control without use of antiretroviral therapy (ART) [38]. VRC01 has the capacity to neutralize a broad range of HIV-1 strains in vitro (Section 2.3) and has conferred protection against simian-human immunodeficiency virus (SHIV) challenges in nonhuman primate (NHP) studies [39-48] (Section 2.8). It has an acceptable safety profile, as seen in previous phase 1 studies (Section 2.9).

In addition to potentially developing a new HIV prevention modality, evaluating the preventive efficacy of mAbs can be expected to inform future HIV vaccine development. An important requisite for designing vaccines that elicit bNabs is determining the level of neutralizing activity required to achieve a reasonable degree of protection in humans. It will also be important to know whether such levels vary by route of infection or neutralizing sensitivity of the infecting isolate. Notably, VRC01 contains the Fc portion of IgG1 and has demonstrated other effector functions. Evaluating the role of antibody-mediated effector functions (eg, antibody-dependent cellular cytotoxicity [ADCC], antibody-dependent cellular phagocytosis [ADCP], antibody-dependent cell-mediated viral inhibition [ADCVI], antibody-mediated virion capture in mucus, or inhibition of viral translocation across epithelial barriers, etc.) in protection is also of critical importance (see, eg, [49-52]).

As it is uncertain at present whether administration of VRC01 or any other bNab can prevent HIV-1 acquisition in humans, participants in this study should expect no direct benefit from the study drug.

2.2 bNabs to HIV-1

The last several years have seen a marked increase in the number of well-characterized bNabs to HIV-1. Figure 2-1 shows the names and binding sites of many of these.

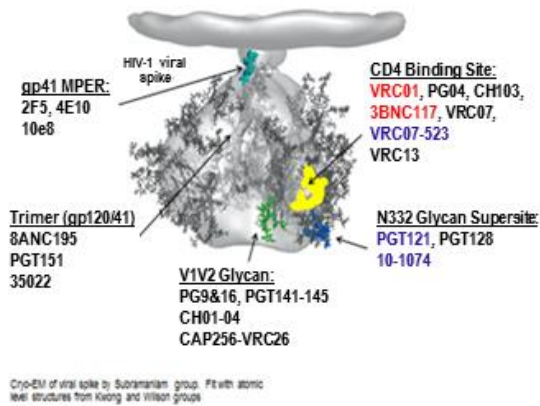


Figure 2-1 Neutralizing antibody epitopes on native Env trimer

As shown in Figure 2-2, several of these antibodies have shown considerable breadth of neutralization in in vitro testing.

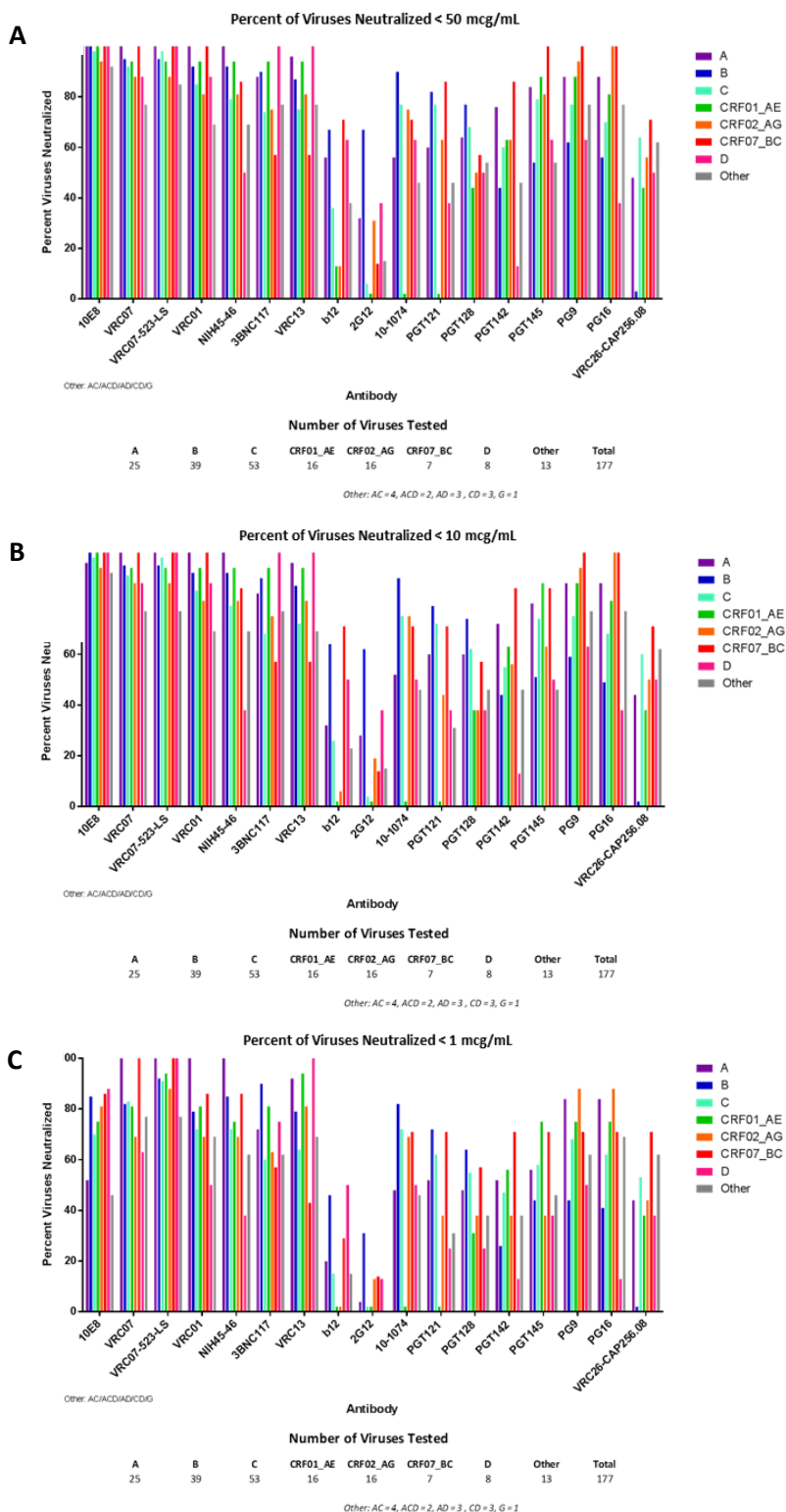


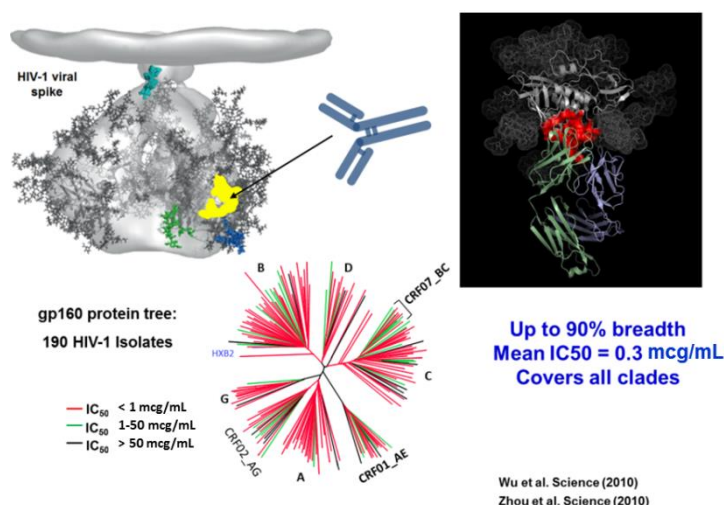
Figure 2-2 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL [31,48,53-56].

Two antibodies to the CD4 binding site of the HIV-1 envelope, VRC01 and 3BNC117 (highlighted in red in Figure 2-1), have entered phase 1 clinical trials.

2.3 VRC01: VRC-HIVMAB060-00-AB

VRC01 is a human mAb, developed by VRC/NIAID/NIH, directed against the CD4-binding site of HIV-1. The bulk lot of the drug substance was manufactured under current Good Manufacturing Practice (cGMP) conditions in a Chinese Hamster Ovary (CHO) cell line and the drug product vials were filled and labeled at the VRC Vaccine Pilot Plant (Frederick, Maryland, USA) operated by Leidos Biomedical Research, Inc. (formerly SAIC-Frederick), Frederick, Maryland (USA). Product is vialled at a concentration of 100 mg/mL VRC01 in formulation buffer containing 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. VRC01 was produced using recombinant DNA technology. Briefly, using polymerase chain reaction (PCR) amplification and cloning of the heavy and light chain variable region genes, a mAb was initially isolated from a single B cell from an HIV-1–infected subject who displayed bNabs. VRC01 is an IgG1 antibody and is highly somatically mutated from the germ-line precursor.

The VRC01 antibody has been well characterized preclinically and has demonstrated favorable characteristics in potency and half-life [18]. In addition, it has demonstrated protection in NHP challenge studies (see Section 2.8.1 below). Figure 2-2 shows graphically the impressive breadth of VRC01, with 90% of 190 HIV-1 isolates across all clades tested showing sensitivity to neutralization by VRC01. As shown in Figure 2-3, VRC01 has a 50% inhibitory concentration (IC_{50}) of < 50 mcg/mL against 91% of primary HIV-1 isolates and IC_{50} < 1 mcg/mL against 72% of HIV-1 isolates. Notably, the IC_{50} for the vast majority of HIV-1 isolates tested is < 1 mcg/mL; the geometric mean IC_{50} for HIV-1 strains from all clades tested is 0.33 mcg/mL.



Virus clade	Number of viruses	$IC_{50} < 50$ mcg/mL	$IC_{50} < 10$ mcg/mL	$IC_{50} < 1$ mcg/mL
A	22	100%	100%	95%
B	49	96%	94%	80%
C	38	87%	84%	66%
D	8	88%	88%	50%
CRF01_AE	18	89%	83%	61%
CRF02_AG	16	81%	75%	56%
G	10	90%	90%	90%
CRF07_BC	11	100%	91%	45%
Other	18	83%	83%	78%
Total	190	91%	88%	72%

Figure 2-3 CD4 binding site antibody: VRC01 [17,18]

Details on VRC01 composition and manufacturing can be found in the investigator's brochure (IB).

2.4 Trial design rationale

Several considerations inform the design of this test-of-concept phase 2b study. The first is to establish that passive administration of bNabs can block HIV acquisition. Based on data from in vitro neutralization studies, the NHP challenge studies described below, and pharmacokinetic (PK) data from the phase 1 clinical trial VRC 602, the doses selected are designed to elucidate the activity of the antibody across a range of serum concentrations in a diverse population of at-risk persons in multiple geographic regions of the world. The study is designed to define the optimal dosage for widespread use of the antibody or its subsequent derivatives as well as to benchmark the types of effector functions associated with efficacy, thus constituting an important bridge to other types of bNabs and other bNab delivery systems.

Inclusion of different doses (ie, in a 3-arm study) is important for a number of reasons. First, while the in vitro and NHP challenge data are informative, the VRC01 antibody serum level required to provide protection against HIV-1 infection in humans is unknown. Some studies suggest that transmitted-founder HIV strains may be more sensitive to neutralization than other strains (particularly by VRC01) [57,58], and therefore potentially susceptible to even lower antibody doses than those suggested by SHIV challenge studies in NHP. It must also be recognized that for utility purposes, the

lowest challenge doses used in the NHP model likely exceed natural exposure in the majority of transmissions in humans.

Defining the lowest efficacious VRC01 dose is essential for establishing a target product profile (TPP), including optimal dosing for clinical use, for this antibody and its derivatives. Typically, higher doses of drug products are associated with lower tolerability due to side effect profiles or operational features such as length of drug administration time (eg, IV infusion time). At present the high dose (30 mg/kg) cannot be administered subcutaneously (SC), limiting the feasibility of long-term clinical use. The extreme difficulty of scaling IV administration to the populations most in need of protection against HIV infection and the complexity and cost of manufacturing mAbs would severely limit implementation of this potentially important HIV prevention tool if higher doses are required for efficacy. Therefore, it is important to evaluate the efficacy achieved at lower antibody concentrations. That lower doses of mAbs may prevent HIV acquisition is supported by the high percentage of isolates susceptible in vitro to antibody concentrations as low as 1 mcg/mL of VRC01, 1/10 the mean trough level anticipated with 30 mg/kg VRC01 dosing every 8 weeks.

Including a range of doses in this study also facilitates evaluation of antibody effector functions, in addition to neutralization, that are associated with protection (eg, virion binding, ADCC, ADCP). Note that the relationship of these important functions to neutralization is not linear and therefore cannot be inferred directly. This information will have important implications for the development of other bNabs and other biomedical HIV prevention modalities.

Hence, in addition to providing a test of concept for AMP for HIV, if breakthrough infections are observed, the data generated by this trial will help guide development of functionally-enhanced mAbs and of long-term delivery strategies (eg, vaccine immunogen or vectored immunoprophylaxis). This trial affords a unique opportunity to correlate serum antibody levels and the potency of effector functions with protective efficacy in a trial in which these parameters can be measured close to the time of HIV acquisition, providing benchmarks for vaccine development and helping define “targets” of antibody effector mechanisms for protein or viral vector based vaccines. The data will also provide critical information by which to identify which NHP models (eg, SHIV challenge stocks) are most predictive of bNab efficacy in humans.

As it is entirely uncertain at present whether administration of VRC01 or any other bNab can prevent HIV-1 acquisition in humans, participants in this study should expect no direct benefit from the study drug.

2.4.1 Cohort selection

The study will be conducted in 2 cohorts, each drawn from a population at high risk of HIV acquisition. The first cohort will comprise 2400 men and TG in North and South America who have anal sex with men or TG partners; the second cohort will comprise 1500 sexually active women in sub-Saharan Africa. The trial sample size is designed to provide 90% power to detect a prevention efficacy (PE) of 60% (rejecting the null hypothesis of 0% PE) in each cohort, based on reasonable assumptions regarding background HIV-1 incidence, retention, and frequency of infusions.

With respect to HIV incidence, over the past 25 years, MSM and TG who have sex with men have been the only risk groups in the US for which estimated HIV incidence has

increased, with more recent increases in incidence noted particularly among young MSM of color [59,60]. In 2013, the estimated rate of new HIV diagnoses among Hispanic/Latino males was three times the rate of White males and 79% of these infections were attributed to male-to-male sexual intercourse [61]. Among gay and bisexual men, Black MSM – especially those between the ages of 13 and 24 – are most affected by HIV [62]. Indeed, the HPTN 061 study found incidence of almost 6% annually among young Black MSM [63]; this is far higher than HIV incidence reported previously in White MSM. A second study found higher HIV prevalence in Black MSM than in White MSM [64].

HIV prevalence in sub-Saharan Africa continues to be higher than anywhere else in the world, with acquisition rates among heterosexual women as high as 6-8% annually in some locations [65]. In recent clinical trials in southern Africa, annual HIV-1 incidence rates of 1.9-9.1% have been observed among sexually-active women [66-72].

2.4.2 Dose and schedule

Within each study cohort, an equal number of study participants will be randomized to receive VRC01 mAb by IV infusion at a dose of 10 mg/kg or 30 mg/kg every 8 weeks, or to receive control infusions every 8 weeks. The 8 week infusion interval represents approximately 4 half-lives of the study drug (half-life ~14 days based on previous clinical testing; see the IB).

Infusions will continue for 72 weeks for all groups, with a final primary follow-up visit (without infusion) at week 80 and an additional 12 weeks of follow-up without infusions. Hence, the study duration for each participant is 92 weeks, slightly over 21 months (approximately 1.75 years).

Projected serum concentrations of VRC01 are shown in Figure 2-4. This figure plots predicted median VRC01 serum concentrations over time based on PK models for VRC01 administered at 10 mg/kg every 8 weeks (Panel A) and for VRC01 administered at 30 mg/kg every 8 weeks (Panel B). The plots include shaded regions illustrating time regions where the study participants have serum concentrations in low, medium, and high ranges. Based on in vitro neutralization studies (see Section 2.3) and NHP challenge studies (see Section 2.8.1) and assuming that these accurately predict protection in humans, the expected trough levels of VRC01 are projected to be an order of magnitude higher than the levels required to protect against a majority of circulating HIV-1 strains.

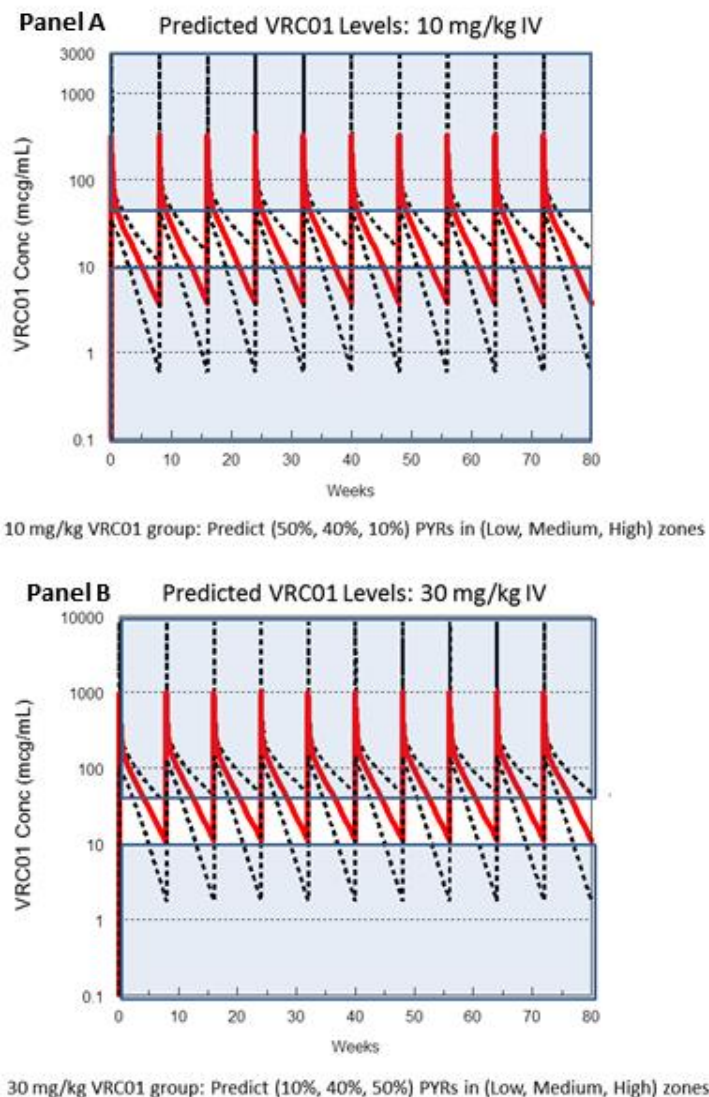


Figure 2-4 Predicted VRC01 serum concentrations over time. Panel A: Predicted VRC01 median serum concentration over time (solid lines) for 10 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72, with 95% confidence intervals (CI) (dashed lines). The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. Panel B: Predicted median VRC01 serum concentration over time for 30 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72. The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. PYR = person-year at risk.

There is a substantial overlap in the mAb concentrations between the low and high dose groups during a considerable period of time after each infusion. This is shown in Figure 2-5.

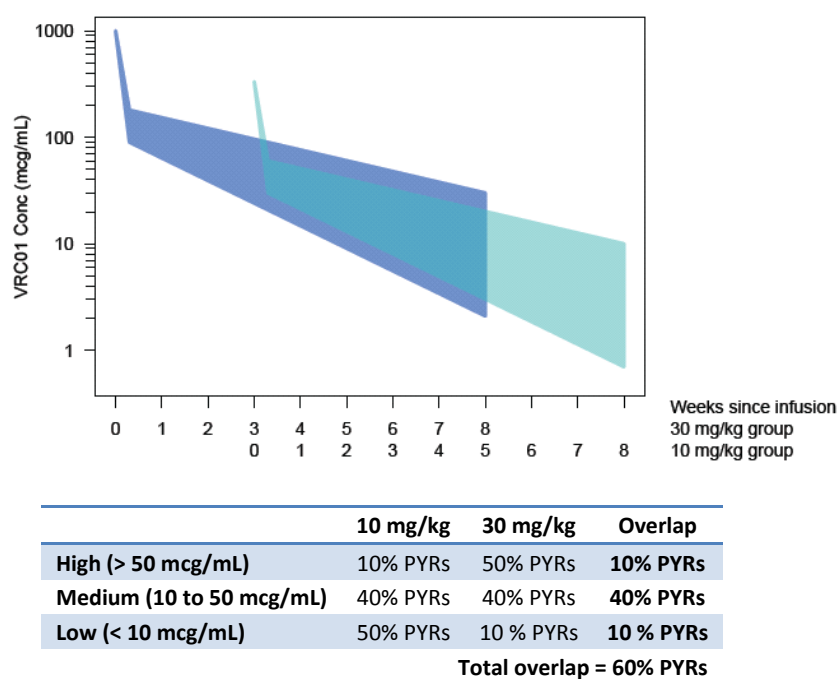


Figure 2-5 Projected overlap in serum VRC01 concentrations and PYRs of HIV exposure between high dose (30 mg/kg) and low dose (10 mg/kg) VRC01 administration

2.4.3 Choice of control

Sodium Chloride for Injection 0.9%, USP (referred to as Control) administered IV at a volume of 150 mL will serve as an inert control.

Use of a placebo control in this trial is warranted based on the scientific and public health importance of the questions it seeks to answer, the necessity of a placebo control in order to assess VRC01 efficacy in preventing HIV-1 infection, and an acceptable risk/benefit ratio considering the minimal risk associated with the placebo control selected and its administration via a procedure commonly used in clinical care. In addition, the placebo control is essential to maintain double-blinding to ensure unbiased assessments of study product safety and efficacy, and the use of the placebo control is disclosed fully to study participants (see Section 10 of Appendix A). Hence, this trial meets the standards commonly required for ethical use of placebo controls in clinical trials [73-75].

2.4.4 HIV diagnostic testing

HIV diagnostic testing will be scheduled at least every four weeks and at any time following participant report of possible exposure during the study. See Section 8 for further detail on HIV-infection assessment. Participants who are diagnosed with HIV infection after enrollment will not receive additional infusions. Infusions will also be permanently discontinued for participants who have 2 reactive HIV tests, even if subsequent testing indicated that the participant is not HIV infected. Based on the schedule of testing, it is possible that a newly infected participant may receive an infusion of VRC01 (or Control). This does not appear to pose a safety risk for participants based on existing preclinical, clinical, and in vitro data. Specifically, passively-infused VRC01 given to NHP on Day 7 after SHIV SF162P3 infection reduces viremia and does not

cause clinical harm (see IB). Additionally, passive transfer of neutralizing antibodies (at non-protective levels) prior to infection improved control of SHIV viremia and was associated with early NAb development in infected infant macaques [76]. Furthermore, VRC01 has been evaluated in viremic and aviremic HIV-infected participants (see Section 2.9.1). VRC01 administration is associated with statistically significant transient reductions in HIV viral load in adults with chronic HIV infection (see IB), and HIV variants that escape from in vitro VRC01 neutralization have reduced viral fitness [77]. Studies evaluating VRC01 in acutely infected subjects are being initiated based on these data.

2.4.5 Trial monitoring

As this is the first large-scale phase 2b study with IV administration of a biomedical intervention for prevention of sexual HIV-1 transmission, the trial design includes an early feasibility check. After approximately 240 participants have completed the Week 32 visit, a treatment-blinded analysis of infusion feasibility will be conducted and reported to the DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq 80\%$ of those 240 participants remain engaged in the trial and have not declined further infusions. Enrollment will not be paused for this feasibility assessment, with the condition that no more than approximately 25% of the planned full study population will be enrolled prior to completion of the assessment.

In addition to the feasibility assessment, the study design includes sequential monitoring for potential harm, nonefficacy, high efficacy, and operational futility. Following monitoring procedures developed and implemented for the HVTN 505 phase 2b vaccine efficacy trial, potential harm monitoring is conducted separately for each mAb group and is maximally vigilant by testing for a higher HIV infection rate in the mAb group versus the control group after each HIV infection and providing the results to the DSMB after each infection. This ensures that any potential risk of increased HIV acquisition (negative prevention efficacy [PE]) with either mAb group would be detected as early as possible, such that a mAb group could be expeditiously discontinued. In addition, the operating characteristics of the trial (Figure 4-5, Figure 4-6, Table 4-2, Table 4-3) show that this potential harm-monitoring approach has a low risk of stopping the study prematurely if the true PE is 0% or higher. The nonefficacy monitoring is conducted separately for each cohort and is conducted approximately every 4 months, and is initiated at the timepoint at which in one of the cohorts a point estimate of zero for PE would correspond to the nominal upper 95% confidence interval for PE equaling the stopping boundary of 40% [78].

At the 4-month intervals, statistical interim analysis reports are provided to the DSMB. While the monitoring guidelines operate separately for the American and African cohorts, the DSMB receives the totality of the data so that it can take account of all information in making its recommendations. Gilbert et al [79] describe the conceptual approach to the sequential monitoring of PE, where the implementation for the current trial is slightly different. Additional information is provided in Section 4.7. Full details regarding implementation of monitoring for this trial are contained in a separate trial monitoring plan.

2.5 Combination Prevention for HIV acquisition

In the context of the study, participants in all arms will be provided with standard-of-care HIV prevention. This generally includes behavioral risk reduction counseling, condoms and lubricant, counseling and referral for PEP, and, where appropriate, access to oral PrEP (see below). We anticipate that these activities will reduce HIV incidence below historical levels for each risk group and the contribution of these efforts will be monitored. Further details on these efforts are provided in the HVTN 703/HPTN 081 Study Specific Procedures (SSP).

2.5.1 PrEP

In recent years, several clinical trials have assessed the efficacy of ARVs taken prophylactically in reducing HIV transmission and acquisition. In some populations, oral ARVs have demonstrated striking efficacy; in other populations the results have been less encouraging.

2.5.1.1 MSM

In 2010, the iPrEx study demonstrated moderate efficacy of once-daily oral FTC/TDF for HIV PrEP among at-risk men and male-to-female (MTF) TG in South America, South Africa, Thailand, and the US [6]. Notably, efficacy estimates were much higher for trial participants whose laboratory assays indicated that they were compliant with the PrEP regimen. In 2015, the PROUD open-label trial confirmed that once daily FTC/TDF was highly efficacious for HIV prevention in MSM who received the drug in sexual health clinics in England [80] and the IPERGAY trial, conducted in France and Canada, demonstrated high efficacy for pericoital use of FTC/TDF in at-risk men who had frequent sex with men [81].

2.5.1.2 Heterosexual men and women

In 2011, the US Centers for Disease Control (CDC) TDF 2 trial demonstrated efficacy of once-daily FTC/TDF in sexually-active heterosexual men and women in Botswana [82]. The Partners PrEP trial demonstrated efficacy of once-daily oral TDF and once-daily FTC/TDF for HIV-uninfected serodiscordant partners in Kenya and Uganda [83].

2.5.1.3 Women at risk of HIV acquisition

Comparable levels of efficacy have not been demonstrated in trials evaluating topical or oral tenofovir (TFV)-based regimens in populations of at-risk women in Africa outside of serodiscordant couples. While the CAPRISA 004 trial demonstrated a 39% reduction in HIV infection with pericoital application of TFV 1% vaginal gel among at-risk women in South Africa [70], efficacy was not seen in the recently completed FACTS 001 trial conducted among young South African women [84]. In 2011 the FEM-PrEP trial was stopped early because of lack of efficacy of once daily oral FTC/TDF among at-risk women in Kenya, South Africa, and Tanzania [71]. In 2011 the VOICE trial, conducted in Uganda, South Africa, and Zimbabwe, reported no efficacy of once daily oral TDF or TFV 1% gel; in 2013, this trial reported no efficacy for once daily oral FTC/TDF [85]. These clinical trial results are summarized in Table 2-1. Poor adherence to the regimens under evaluation appeared to be a significant barrier to evaluating efficacy in both the FEM-PrEP and VOICE studies. In addition, there is reason for concern that limited metabolism of ARVs in female mucosal tissues may compromise efficacy in women [86].

Table 2-1 PrEP trial summary

Study population	Study	Locations	Regimen	Efficacy (Est.)
MSM & TGW	iPrEx [6]	South America, South Africa, Thailand, US	Daily oral FTC/TDF	44%
	PROUD [80]	England	Daily oral FTC/TDF	86%
	Ipergay [81]	France, Canada	Pericoital oral FTC/TDF	86%
Heterosexual men & women	TDF 2 [82]	Botswana	Daily oral FTC/TDF	62%
Serodiscordant couples	Partners PrEP [83]	Kenya, Uganda	Daily oral FTC/TDF or TDF	67%
Women at risk	CAPRISA 004 [70]	South Africa	Daily TFV 1% gel	39%
	Fem-PrEP [71]	Kenya, South Africa, Tanzania	Daily oral FTC/TDF	6%
	VOICE [85]	South Africa, Uganda, Zimbabwe	Daily oral TDF Daily oral FTC/TDF Daily topical TFV 1% gel	-49% -4.4% 14.5%
	FACTS 001 [84]	South Africa	Daily TFV 1% gel	0%

2.5.1.4 Guidance to date on PrEP

In 2011, the US CDC issued interim guidelines for use of FTC/TDF as PrEP for high-risk MSM [87]. In 2012, the US FDA approved FTC/TDF for HIV prophylaxis in persons at high risk for HIV infection. That same year, the World Health Organization (WHO) issued guidance on the use of PrEP for serodiscordant couples and for men and TG women who have sex with men [88]. In 2014, the US CDC issued a further PrEP recommendation and a Clinical Provider Supplement [89,90]. PrEP use has since been incorporated into WHO guidelines for ARV use for HIV treatment and prevention [91]. Notably, guidance documents to date have not, in general, recommended PrEP for women at risk for HIV acquisition through sexual contact unless they are in serodiscordant relationships or have other specific risk factors for HIV acquisition. Similarly, many local and national regulatory authorities have not authorized PrEP use among women.

Current standards of care for HIV prevention are strikingly different for different regions and risk groups. It is anticipated that standards of HIV prevention will continue to evolve in the coming years and it is also expected that diversity across geographic regions and risk groups in recommendations for HIV prevention standards will persist. Arrangements for provision of PrEP in this trial will take into account current evidence regarding PrEP efficacy in the populations to be enrolled in this trial, community consultation, guidance from international/regional/national/local and other regulatory authorities, and advice from persons/groups with bioethics and human subjects protection expertise.

2.6 Plans for future product development and testing

VRC01 is considered to have potential value for both preventive and therapeutic purposes across broad geographic regions of the HIV-1 epidemic. The product was initially evaluated in phase 1 studies to characterize PK and distribution in HIV-infected and HIV-uninfected adults (VRC 601 and 602, respectively; see Sections 2.9.1 and 2.9.2) and PK and safety for multiple administrations under several route and dosing regimens are being evaluated currently (HVTN 104; see Section 2.9.3). In parallel, IMPAACT P1112 will evaluate the safety of VRC01 in high-risk infants born to HIV-infected mothers; data from this study will support a future evaluation of the efficacy of VRC01 administered to high-risk infants shortly after birth and continued through the period of breast-feeding for prevention of mother-to-child HIV transmission (PMTCT).

The development of VRC01 for clinical use depends on a number of factors, the most critical of which is the level of efficacy demonstrated by the current study. If the antibody proves to be highly effective at preventing HIV-1 infection, its development will depend on identifying a partner able to provide large-scale manufacturing. Other factors that could influence advanced development of VRC01 include: 1) the potential for improving the potency of the product to allow use at a lower dose and perhaps by an SC route, 2) the potential for increasing the half-life of the product to allow less frequent dosing, and 3) the potential to use VRC01 in combination with other neutralizing mAbs to increase breadth of coverage. Efforts to address these issues are proceeding in parallel with the current study, but the outcome of the current study will have the greatest influence on the future clinical use of VRC01 in adult prevention or PMTCT.

2.7 Preclinical safety studies

2.7.1 Preclinical toxicology and PK study of VRC01 in rats

Table 2-2 Summary of preclinical studies

Study number	Product	Type of study	Animal	N	Dose groups	Route	Schedule
SRI No M896-11	VRC-HIVMAB060-00-AB	Repeat dose toxicity	Sprague-Dawley rats	10m, 10f each 50m, 50f total	Vehicle* 4mg/kg IV 40 mg/kg IV 400 mg/kg IV 40 mg/kg SC	IV & SC	D1, D8
SRI No M896-11	VRC-HIVMAB060-00-AB	Single-dose PK	Sprague-Dawley rats	9m, 9f each 27m, 27f total	4 mg/kg IV 40 mg/kg IV 40 mg/kg SC	IV & SC	D1

* Vehicle consists of VRC01 formulation buffer.

A repeat dose toxicity study of IV and SC administration and a single dose PK study was performed by SRI International (Menlo Park, CA) with VRC01 in male and female Sprague-Dawley rats in accordance with US FDA “Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies” (Table 2-2). This study was conducted with a pre-GMP pilot lot of VRC01 manufactured at smaller scale using a similar purification process to that of the GMP clinical grade drug product.

For the safety assessment, various doses of VRC01 (4 mg/kg, 40 mg/kg, or 400 mg/kg) or a comparable control vehicle was administered by tail vein infusion on Days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via SC administration to the dorsal scapular region on Days 1 and 8. Each group contained 10 male and 10 female rats. Five animals of each sex were sacrificed on Day 9, one day after the second administration; the remaining animals were sacrificed on Day 30, 22 days after the second administration.

Results obtained showed that both routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, infusion site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate aminotransferase (AST) and alkaline phosphatase (ALP)

on Day 9. By Day 30, AST values had returned to normal, and ALP values were returning to normal.

Other than red discoloration of the administration site in one male in the SC group on Day 9, there were no other gross necropsy observations attributable to VRC01 administration. There were no histopathology findings that were considered related to IV administration of VRC01.

The pre-specified IV dose studied in rats was 400 mg/kg and SC was 40 mg/kg, which will greatly exceed the dose levels in the adult clinical studies. A “no observed effect level” (NOEL) was not determined in this study because transient elevations of AST and ALP were observed on Day 9 after IV administration and transient inflammation at the dose site was observed on Day 9 after SC administration. Because the elevated AST and ALP levels were transient and minor and did not correlate with histopathology findings, the no observed adverse effect level (NOAEL) for VRC01 by the IV route of administration in rats was 400 mg/kg, the highest dose used in this study.

For the PK analysis, 3 groups of rats (9 males and 9 females in each group) received VRC01 on Day 1 at 4 mg/kg IV, 40 mg/kg IV, and 40 mg/kg SC respectively. VRC01 levels in serum were determined using an enzyme-linked immunosorbent assay (ELISA) with samples collected predose from each animal and from an additional 3 males and 3 females to provide untreated control serum. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following postdose timepoints: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life was about 10 days, with clearance of approximately 20 mL/day/kg and volume of distribution that was about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. VRC01 administration by the SC route resulted in mean peak serum levels at 7 days for male or 3 days for female animals. The maximum serum concentration and area under the concentration-time curve to the last timepoint values were lower when 40 mg/kg was administered by the SC route compared with the IV route. The bioavailability of 40 mg/kg VRC01 administered by the SC route was estimated to be 31.4% (males) and 42.3% (females). After the peak concentration of VRC01 was achieved in the SC group, the serum levels decreased much more rapidly from 7 to 14 days than they did in the IV groups, and VRC01 concentrations in the SC group were not quantifiable at timepoints after 14 days. These data indicate that clearance of VRC01 in rats was markedly enhanced when it was administered by the SC route. The development of anti-drug antibodies that contribute to an increased rate of clearance is often observed in preclinical safety studies of protein-based test articles when they are not tested in the species of origin. Although immunogenicity was not examined in this study, the presence of such antibodies might have contributed to the increased rate of clearance of VRC01 after SC administration that was observed in this study [92,93].

2.7.2 Tissue cross reactivity GLP study of VRC01 with human tissues in vitro

A tissue cross-reactivity study of VRC01 using normal adult and neonatal human tissues in vitro (Testing Facility Study No. A255-12) was performed by Charles River Laboratories (Reno, NV) in accordance with U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies” (GLP). The tissue panels used as the test system for this *in vitro* cross-reactivity study included all of the tissues on the “Suggested list of human

tissues to be used for immunohistochemical or cytochemical investigations of cross reactivity of monoclonal antibodies” in Annex I of the “European Medicines Agency Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use on December 18, 2008” and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997).” In addition, the tissue cross-reactivity study used additional neonate/infant tissues suggested by the FDA to support future trials in infants.

To determine the cross-reactivity of VRC01 binding, VRC01 was applied to cryosections from a full panel of tissues from normal human adults and a limited panel of human neonatal tissues, immunohistochemically detected using a biotinylated rabbit anti-human IgG secondary antibody, and binding was visualized with a streptavidin-horseradish peroxidase complex and a diaminobenzidine chromogen substrate. VRC01 binding was evaluated at concentrations of 5 and 50 mcg/mL.

Specific VRC01 staining was not observed in any normal adult human or neonatal human tissues evaluated. Therefore, in vitro evaluation of cross-reactivity in tissue specimens did not identify potential tissue sites or organ systems to more thoroughly evaluate in subsequent preclinical studies, and it supports the future use of VRC01 in humans.

2.7.3 Other toxicity studies

Several in vitro studies were conducted to assess antibody activity against self-antigens by VRC01. Several anti-HIV neutralizing mAbs will cross-react to lipid or nuclear antigens or Hep-2 cells [94,95]. Anti-lipid binding activity is understandable when considering that the HIV-1 gp41 protein is membrane-spanning and the epitopes (MPER: Membrane-Proximal External Region) recognized by some mAbs (eg, 4E10 and 2F5) are membrane-proximal and likely extend into the membrane itself. Therefore, the ability (or lack thereof) of VRC01 to cross-react with lipids was assessed in collaboration with Dr. Barton Haynes of Duke University. Binding of antibody to cardiolipin was assessed in a luminescent assay, expressed in relative units. VRC01 was compared to 4E10, an anti-gp41 mAb known to bind to cardiolipin and nuclear antigens, and Synagis, a licensed anti-RSV antibody used as a negative control. Synagis is included because it is the licensed mAb product most analogous to the intended clinical use of the VRC mAb [12].

Individual studies are summarized in Table 2-3. Unlike other anti-HIV neutralizing mAbs, VRC01 does not react to phospholipids or anti-nuclear antigens or Hep-2 cells. Additional details are provided in the IB.

Table 2-3 In vitro preclinical safety studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC01 does not react to phospholipids
Assessment of anti-nuclear antigen reactivity	VRC01 does not react with nuclear antigens
Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT)	VRC01 does not impact aPTT by binding phospholipids
Assessment of Binding to a Human Cell Line by Immunohistochemistry	Fluorescently labeled VRC01 does not bind Hep-2 cells

2.8 Nonhuman primate (NHP) studies of VRC01

Several non-Good Laboratory Practices (ie, non-GLP) studies of VRC01 have been completed in NHP to assess for preclinical evidence of potential efficacy for prevention of HIV infection. Table 2-4 summarizes the studies performed.

Table 2-4 Summary of NHP pharmacology and challenge studies

Study	Product	Animal	N	Dose/Route	Infusion schedule	Challenge route	Challenge stock/dose	Challenge schedule
Pharmacology	VRC01 (Pilot lot)	Rhesus macaques	4f 4f	40 mg/kg IV 40 mg/kg SC	Day 0	NA	NA	NA
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4m 4m 4m	5 mg/kg IV 20 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-SF162P3 (300 TCID ₅₀ *)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4f 4f	20 mg/kg IV Human IgG IV (control)	Day 0	Intravaginal	SHIV-SF162P3 (300 TCID ₅₀)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	6m 6m 4m 16m 14m	20 mg/kg IV 5 mg/kg IV 1.25 mg/kg IV 0.3 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-BaL (TCID ₅₀ 12,800 in TZM-bl)	Day 2 postinfusion

*TCID₅₀ = 50% tissue culture infectious dose

In the pharmacology study, plasma and mucosal (ie, rectal, vaginal, and nasal) samples were collected at frequent intervals through Day 28. A dose of 40 mg/kg IV or SC in female rhesus macaques resulted in plasma concentration of VRC01 exceeding 50 mcg/mL in 7 of 8 animals at Day 14 and greater than 10 mcg/mL in 7 of 8 animals at Day 28.

Please see the VRC01 IB for more details.

2.8.1 Protection against challenge in NHP models

Both neutralizing and non-neutralizing antibodies to HIV and SIV have been shown to protect against experimental challenge in the NHP model [39-41,96-100]. In these studies the degree of protection has varied with the neutralizing potency of the antibodies and with the dose, route, and sensitivity of the challenge stocks. Low antibody concentrations have in some instances been quite protective, especially against repeat low-dose mucosal challenges [43,44]. However, neutralization-resistant SHIVs have been developed and have been shown to be resistant to protection [101,102]. This has permitted estimation of neutralization titers for different mAbs against SHIVs representing a broad range of neutralization resistance.

VRC01 has been tested in several NHP challenge experiments (see Table 2-4). In a rectal challenge model with SHIV BaLP4, a dose of 20 mg/kg IV protected 6/6 NHP; a 5 mg/kg IV dose protected 6/6; and a 0.3 mg/kg IV dose protected 2/6 [46]. Using a more resistant SHIV-162P3 challenge, a 20 mg/kg IV dose protected all 4 male animals from rectal challenge and all 4 female animals from vaginal challenge [46]. Analyses of the combined data from the NHP challenge studies show complete protection against SHIV162P3 challenge at a VRC01 plasma concentration of 50 mcg/ml and partial protection (IC₅₀ [50% inhibitory concentration]) at 20 mcg/mL. For the more sensitive

BaLP4 virus the IC₅₀ is only 1.5 mcg/ml. Based on preclinical studies, an antibody serum concentration of about 40 to 50 mcg/mL is projected to provide protection against the vast majority of circulating strains of HIV [103]. In the NHP studies, both the virus sensitivity and serum antibody titers appear to influence protection from mucosal challenge. A summary of serum concentrations associated with protection against diverse SHIV strains of varying resistance to neutralization is shown in Figure 2-6.

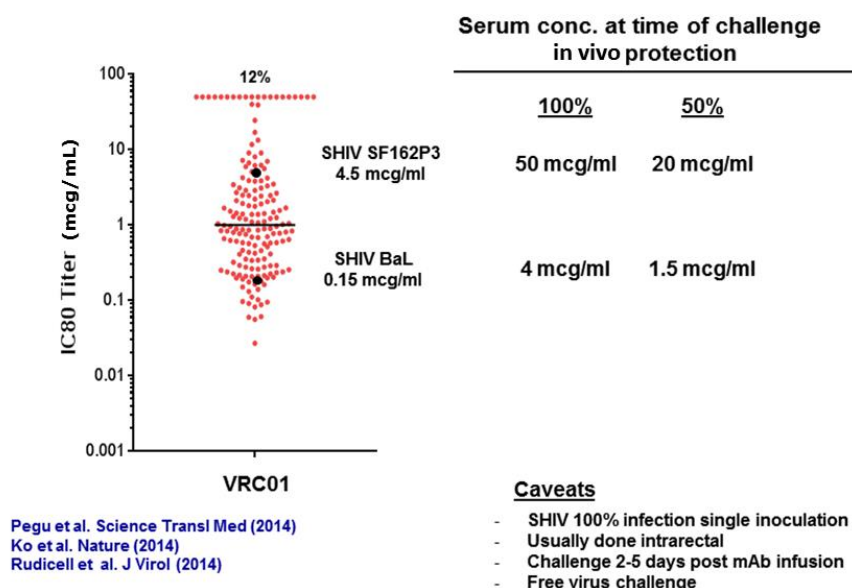


Figure 2-6 VRC01 IC₈₀ values (170 Isolates) and serum concentrations in NHP SHIV challenge studies

It is particularly interesting to note that following administration of VRC01 to NHP, the antibody is found in mucosal tissues (see Figure 2-7), likely a product of active antibody transport to mucosal tissues through neonatal Fc receptor (FcRn) binding [47]. Such transport may differ between the rectal and female genital tracts, which provides additional justification for including 2 separate cohorts in the study (see Table 1-1).

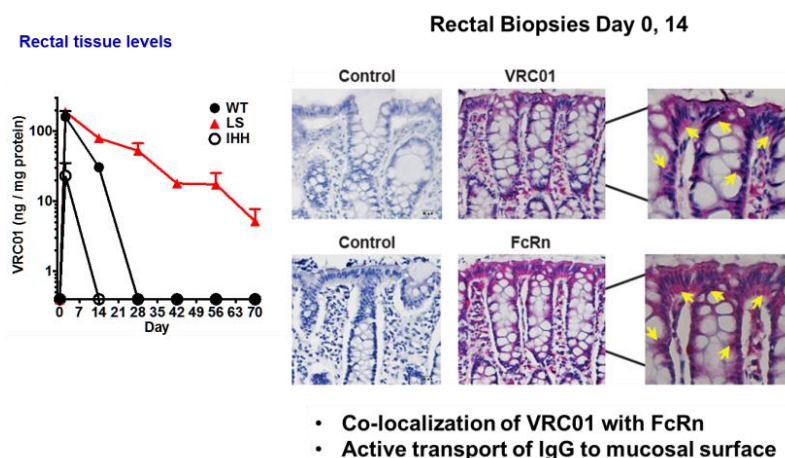


Figure 2-7 VRC01 mucosal pharmacokinetics in rhesus macaques [47]

Please see the VRC01 IB for more details on the NHP challenge studies.

2.9 Phase 1 clinical trial experience

Phase 1 clinical trials of VRC01 are currently underway. Completed studies include first-in-humans dose escalation studies for safety, tolerability, and PK assessments in HIV-infected (VRC 601) and HIV-uninfected (VRC 602) adults. Studies to characterize the neutralizing activity and other functional assays as a function of plasma concentration are also underway.

Both the IV and SC routes of administration have been evaluated. Ultimately, the best route for clinical use may depend upon the age of the recipient (adult or infant), stage of product development, formulation, and important considerations related to volume needed and maintenance of a target VRC01 blood level considered to be in the therapeutic range.

2.9.1 VRC 601

VRC 601 (NCT01950325) titled, “A Phase 1, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults.”

VRC 601 (Table 2-5) was the first study of the VRC01 mAb in HIV-infected participants. It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti-antibody immune responses. VRC 601 opened in September 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and in total, 23 HIV-infected participants, including 15 aviremic ARV-treated participants and 8 viremic non-ARV treated participants, were infused with one or two doses of VRC01 at doses up to 40 mg/kg IV.

Table 2-5 VRC 601 study schema

VRC 601 Dose Groups		VRC01 Administration Schedule	
Group	No. of evaluable participants*	Day 0	Week 4
1	3-5	1 mg/kg IV	1 mg/kg IV
2	3-5	5 mg/kg IV	5 mg/kg IV
3	3-5	5 mg/kg SC	5 mg/kg SC
4	3-5	20 mg/kg IV	20 mg/kg IV
5	3-5	40 mg/kg IV	40 mg/kg IV
Total	15-25	IV doses administered in 100 mL of normal saline over 30-60 minutes. SC doses administered in the minimum volume at 15 mL/hr. *Only participants who begin infusion are evaluable. Only 3 evaluable participants per group will be enrolled into the dose group until the safety review is completed. Additional slots are available, if needed, to have sufficient data for the safety review or to include at least one eligible subject with a detectable viral load later after the dose escalation is complete.	

The first infusion at 1 mg/kg IV was administered in the VRC 601 study on September 30, 2013. Beginning on March 28, 2014, the dose escalation proceeded according to the

schema. The first 40 mg/kg IV administration in this study occurred May 12, 2014 and the last infusion in VRC 601 occurred on April 6, 2015. All IV and/or SC infusions have been well-tolerated with no serious adverse events (SAEs) or dose limiting toxicity.

VRC 601 demonstrated evidence of VRC01-mediated antiviral effect. An interim analysis of the VRC 601 viral load data obtained from 8 viremic adults through April 30, 2015 shows that VRC01 has a statistically significant in vivo virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking antiretroviral therapy (ART) when enrolled into the study and had not started ART during the time period when the viral load data were collected. Six of the eight adult participants had $\geq 1 \log_{10}$ copies/mL decrease in viral load and two participants had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL respectively. These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load postinfusion days 5 to 16;
- The median time to reach $\geq 0.5 \log_{10}$ decrease in viral load is 5 days; and,
- The median time to greatest decrease in viral load is 7 days.

A 0.5 $\log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ART. To have clinical benefit, such a change would need to be sustained. In VRC 601, participants were administered only one dose of VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected. However, the data demonstrate a VRC01 mediated anti-viral effect.

2.9.2 VRC 602

VRC 602 (NCT01993706) is titled, “*A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults.*”

VRC 602 was the first study of the VRC01 mAb in HIV-uninfected adults. It was a dose-escalation study to examine safety, tolerability, dose, and PK of VRC01. VRC 602 opened in December 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and the final infusion was administered in August 2014.

As shown in Table 2-6, there were 3 open-label, dose escalation groups (Groups 1, 2, and 3) for IV administration and 1 double-blinded, placebo-controlled group (Group 4) for SC administration.

Table 2-6 VRC 602 study schema

VRC 602 Groups			VRC01 Administration Schedule	
Group	Initial Enrollments	Additional Enrollments	Day 0	Week 4
1	3	2	5 mg/kg IV	5 mg/kg IV
2	3	2	20 mg/kg IV	20 mg/kg IV
3	3	2	40 mg/kg IV	40 mg/kg IV
4	SC administration			
4A	3	2	5 mg/kg SC	5 mg/kg SC
4B	3	2	Placebo SC	Placebo SC
Total		25	20 participants treated with VRC01 at different dosage levels and 5 participants treated with placebo administered SC	
IV doses administered in 100 mL of normal saline over 1 hr. First SC dose administered at about 15 mL/hr via SC infusion pump; subject option for second dose administration (Week 4) by direct SC injection with needle and syringe.				

All IV and/or SC infusions were well-tolerated with no SAEs or dose limiting toxicity.

PK analysis from VRC 602 revealed a VRC01 terminal half-life of 15 days across all IV infused dose groups. After the first infusion, 28-day trough levels were 35 mcg/mL and 57 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. Following the second infusion, the 28-day trough values rose to 57 mcg/mL and 89 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively.

2.9.3 HVTN 104

HVTN 104, titled *A phase 1 clinical trial to evaluate the safety and drug levels of a human monoclonal antibody, VRC-HIVMAB060-00-AB (VRC01) administered in multiple doses intravenously and subcutaneously in different dosing schedules to healthy, HIV-uninfected adults*, is examining safety profiles and serum levels of 5 different regimens for the IV and SC administration of VRC01 (Table 2-7). IV administration is being evaluated at doses of 10, 20, 30, and 40 mg/kg; SC administration is being tested at 5 mg/kg.

Table 2-7 HVTN 104 study schema

Dose Groups		Study product administration schedule in months (days)											
Group	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	IV placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01
4	12	VRC01 10mg/kg IV				VRC01 10mg/kg IV				VRC01 10mg/kg IV			
5	12	VRC01 30mg/kg IV				VRC01 30mg/kg IV				VRC01 30mg/kg IV			
Total	88	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered by needle and syringe injection											

HVTN 104 is a phase 1 clinical trial designed to evaluate the safety and drug levels of VRC01 administered in multiple intravenous or subcutaneous doses and different dosing schedules to 88 healthy, HIV-uninfected adults. The first participant enrolled in HVTN 104 on September 9, 2014. As of May 15, 2015, 58 low-risk participants (aged 18 to 50 years old) have been enrolled at 6 HVTN CRSs in 4 U.S. cities: Boston, New York, Philadelphia, and Cleveland. The study has 5 arms: Group 1 is evaluating the IV administration of a 40 mg/kg loading dose, with 2 subsequent 20 mg/kg doses given at 8 week intervals. Groups 2, 4, and 5 are evaluating 3 infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg respectively given 8 weeks apart. Group 3 is evaluating 5 mg/kg given every 2 weeks subcutaneously for 24 weeks (which will inform the design of perinatal prophylaxis studies). Secondary aims of HVTN 104 are: (1) to evaluate the kinetics of *in vitro* neutralization in serum of a single VRC01 sensitive virus isolate (TZM.bl assay); (2) to determine whether anti-idiotypic antibody (AIA) can be detected and whether there is a correlation of VRC01 levels and AIA levels in serum; (3) to determine if measurable levels of VRC01 can be found in genital, rectal, and oral secretions; (4) to evaluate the kinetics of *in vitro* neutralization in mucosal secretions of a single VRC01 sensitive virus isolate; and (5) to assess binding of VRC01 to multiple Env proteins.

The infusions and injections have been well tolerated in HVTN 104. Most participants have had no local reaction or mild local reactogenicity from a particular infusion or injection. Most participants had no systemic reactogenicity symptoms after injections or infusions. When present, most symptoms were mild, with malaise/fatigue, myalgias, and headaches being most common. Of 133 AE's as of April 24, 2015, fewer than 10% were considered product-related and no product-related SAE/EAEs were reported. All laboratory-related AEs were Grade 1 and resolved, including: increased transaminases (3), increased creatinine (1), and neutropenia (2). VRC01 administered IV or SC was well-tolerated. At 28 days, after a single 40 mg/kg infusion, serum levels were > 30 mcg/ml (Groups 1 and 2), and at 56 days, levels ranged from ~10 to 30 mcg/ml (Group 2). Giving 20 mg/kg at day 28 after an initial 40 mg/kg infusion produced serum VRC01 levels ranging from ~30 to 100 mcg/ml at day 56 (Group 1).

2.9.4 Safety summary of VRC01

As of May 11, 2015, 111 participants have received one or more study product administrations, including 23 in VRC 601, 28 in VRC 602, and 60 in HVTN 104.

Cumulatively, there have been no expedited safety reports to the FDA or study safety pauses for adverse events and no reactions during the VRC01 or placebo/control product administration that resulted in an incomplete administration.

VRC01 SC or IV administrations are occasionally associated with mild or moderate local reactions of pruritus (itchiness), redness and pain/tenderness, which resolve within a few minutes to a few hours after the administration is completed. When present, most systemic reactions after administration of VRC01 SC or IV are mild and include: malaise, myalgia, headache, chills, nausea and joint pain.

Unsolicited AEs of grade 3 or higher severity and deemed related to study product have not been reported.

Other AEs attributed to study product administration have included mild or moderate AST elevation, alanine aminotransferase (ALT) elevation, creatinine elevation, and decreased neutrophil count. Mild or moderate elevated transaminases were reported in 4 of 21 (19%) HIV-infected participants in VRC 601 (all of whom were taking ARVs). These laboratory changes resolved spontaneously and did not require discontinuation of study product administration. Among HIV-uninfected participants in VRC 602 or HVTN 104, there has been a single grade 1 (mild) transiently elevated ALT assessed as possibly attributed to VRC01 in the VRC 602 study and three grade 1 (mild) transiently elevated ALT/AST values assessed as related to VRC01 in HVTN 104.

In the blinded HVTN 104 trial, there have been two product discontinuations, both in participants receiving subcutaneous administration of VRC01 or placebo. One discontinuation was for a 20-minute episode of chest tightness occurring approximately 25 minutes after SC injection of VRC01 or placebo in a participant who is a chronic smoker on nicotine replacement while smoking. One discontinuation was in a participant who reported a generalized rash that began three days after SC injection of VRC01 or placebo, and resolved after a few hours with ibuprofen and the application of an over-the-counter non-steroidal cream.

Overall, VRC01 administration in the dose range from 1 to 40 mg/kg IV and at 5 mg/kg SC have been assessed as well-tolerated and safe for further evaluation.

2.9.5 Particle formation

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. In previous phase 1 studies, particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. Particle formation upon thawing has no effect on product quality. For additional information, see the IB.

2.10 Potential risks of study products and administration

In a preclinical study performed in rats, there was a small dose-dependent, but transient, increase in AST and ALP, but not in ALT following IV administration. In rats, there were no histopathology findings following IV administration.

Thus far in VRC 601, VRC 602, and HVTN 104 there have been no safety concerns, including no SAEs deemed related to study product. Administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness, and the generation of auto-reactive antibodies; however, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs, which would have a risk of human anti-mouse antibodies [104]. In this regard, as VRC01 is targeted to a viral antigen and is a human mAb, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [104]; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

It is known from published experience with human mAbs directed against the cell surface targets on lymphocytes that infusion of a mAb may be associated with cytokine release, causing a reaction known as “cytokine release syndrome” [105]. “Cytokine release syndrome” and other immune reactions such as tumor lysis syndrome have been observed with administration of chimeric and humanized mAb [104]. Most infusion-related events occur within the first 24 hours after beginning administration. Specifically, with regard to cytokine release syndrome reactions, these most commonly occur within the first few hours of beginning the infusion and are more common with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, cytokine release syndrome is managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate [106]. Severe reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are infrequent and more often associated with mAbs targeted to human proteins or with a non-human mAb, such as a murine mAb [104]. Most infusion-related events occur within the first 24 hours after beginning administration.

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after exposure to the mAb and are noted to be more common with chimeric types of mAb [104]. Serum sickness has not been described with administration of licensed fully human MABs.

There are several FDA-licensed mAbs for which reactions related to the rate of infusion have been described. Some symptoms may be treated by slowing or stopping the infusion.

Other side effects of licensed MABs include infections, thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity [104].

The HVTN laboratory tested plasma from HIV-uninfected individuals that was spiked with VRC01 in a range of concentrations that encompasses those likely to be observed in this clinical trial. VRC01 did not cause a reactive test result using several standard antibody-based HIV-1/2 diagnostic tests used in the US. However, VRC01 is an antibody to an HIV protein, so, it may be theoretically possible for a standard antibody-based HIV diagnostic test to detect VRC01 for a short time period postinfusion or postinjection. However, this has not been observed in clinical studies to date.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling or bleeding at the IV site and, rarely, infection, vein inflammation (phlebitis), or blood clot.

Risks of IV Infusion: The placement of an IV catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized through the use of aseptic techniques during product preparation and administration.

3 Objectives and endpoints

3.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in each of 2 cohorts

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in each of 2 cohorts

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

3.2 Secondary objectives and endpoints

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available post-HIV-infection serum samples

3.3 Exploratory objectives

Exploratory objective 1:

To assess use of FTC/TDF and other ARVs in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF and other ARV use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

4 Statistical considerations

4.1 Outline of the statistical considerations section

The statistical considerations section is organized as follows. Section 4.2 states the primary and secondary efficacy objectives in terms of the target prevention efficacy (PE) parameters that are estimated in the trial, and describes the hypothesis tests regarding these efficacy parameters. Section 4.3 summarizes a statistical rationale for using a 3-arm design, which adds to the scientific rationale provided in Section 2.4. Section 4.4 describes sample size and power considerations for the primary efficacy objectives, which justify the sample size of the trial. Section 4.4 also provides operating characteristics of the trial design for addressing the primary efficacy objective. Section 4.5 describes statistical power available for the secondary objective that compares PE between the two mAb dose groups. Section 4.6 describes statistical power available for detecting safety problems of the mAb in terms of SAEs. Section 4.7 summarizes the approach to monitoring the trial including interim analysis reports provided to the DSMB. Sections 4.8, 4.9, and 4.10 describe ARV assessments, randomization, and blinding, respectively. Section 4.11 describes the approach to statistical analysis, ordered first by the approach to the analysis of PE, and secondly by the approach to the assessment of correlates of protection.

The trial is powered separately for each cohort, that is, for MSM and TG individuals in the Americas and for women in sub-Saharan Africa. Throughout the statistical section “cohort” refers to MSM+TG individuals in the Americas or women in sub-Saharan Africa.

4.2 PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests

For a given cohort, let PE denote the overall PE of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. This PE parameter is defined as

$$PE = [1 - \text{Cumul. incid. ratio (pooled mAb grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%,$$

where the cumulative incidence ratio is the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive the mAb divided by the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive control. PE is the target parameter for the primary analysis of overall PE. Within each cohort separately, the primary analysis tests the null hypothesis

$$H_0: PE \leq 0\% \text{ versus the alternative hypothesis } H_1: PE > 0\%$$

using a 1-sided alpha = 0.025 level test that accounts for sequential monitoring for potential harm, non-efficacy, and high efficacy.

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall PE of the 10 mg/kg mAb group and let PE30 be the overall PE of the 30 mg/kg mAb group, defined as

$$\text{PE10} = [1 - \text{Cumul. incid. ratio (mAb-10 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%$$

and

$$\text{PE30} = [1 - \text{Cumul. incid. ratio (mAb-30 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%.$$

Within each cohort separately, secondary analyses test the null hypotheses

H0: $\text{PE10} \leq 0\%$ versus the alternative hypothesis H1: $\text{PE10} > 0\%$

and

H0: $\text{PE30} \leq 0\%$ versus the alternative hypothesis H1: $\text{PE30} > 0\%$

using 1-sided alpha = 0.025 level tests. No multiplicity correction is done for the two tests, because in this proof-of-concept study there is high utility in increasing statistical power at the expense of a slightly elevated risk of a false positive result.

In addition, for each cohort the following secondary analyses of PE are conducted:

- Assess a dose-response effect by testing the null hypothesis
H0: Cumul. HIV-1 incidence by 80 Wks equal in the 3 groups versus H1: $0 \leq \text{PE10} \leq \text{PE30}$ with at least one strict inequality
- Test the complete null hypothesis that the HIV-1 incidence is the same in the three treatment groups versus the alternative hypothesis that there are some differences
- Test for different HIV-1 incidence between the two mAb groups, where a finding of PE30 significantly greater than PE10 would demonstrate that assignment to a higher mAb dose level causes higher PE

The above hypothesis tests are repeated for PE, PE10, and PE30 defined as above except including both cohorts pooled together in the analysis. Interaction tests are done to assess whether these PE parameters differ by cohort. All analyses that include both cohorts in the analysis allow a separate control group cumulative incidence of HIV-1 infection in the two cohorts (ie, cohort stratified analysis).

4.3 Statistical rationale for the 3-arm design compared to a 2-arm design

An alternative design would compare a single dose and schedule of the VRC01 mAb versus control. However, the 3-arm design allows addressing additional scientific questions and improves the assessment of correlates of protection, without requiring more participants by virtue of the primary analysis being based on the pooled mAb groups

versus control. By providing results about estimated PE10 and estimated PE30 as well as about pooled estimated PE, the trial provides data for modeling of how PE would change given a new dose and/or schedule.

A second advantage of the 3-arm design is that it allows a direct assessment of the causal effect of different mAb infusion doses on HIV-1 incidence based on randomization of treatment assignments (a so-called ‘group-level’ correlate of protection), which can directly prove the concept that a higher mAb dose causes a greater level of protection. In contrast, with a 2-arm design the association between mAb marker characteristics and the level of PE can only be inferred with non-randomized epidemiological analysis approaches for which the results cannot be guaranteed to be free from postrandomization selection bias [107,108]. That is, without a randomization to multiple mAb interventions a result that a mAb characteristic is associated with reduced incidence of HIV-1 infection may not imply that mAb recipients with the characteristic have a higher level of PE. For instance, the implication may fail if participants tend to have fewer HIV-1 exposures during the few weeks after infusion visits compared to during the few weeks before infusion visits, which could possibly occur related to the counseling and informed consent process. Or, the implication may fail if the mAb characteristic marks an intrinsic HIV-1 susceptibility factor that is not caused by administration of the mAb [109-111]. A third advantage of the 3-arm design is that the random assignment of two mAb doses creates greater inter-individual variability in mAb characteristics, which improves statistical power for the assessment of individual-level correlates of protection.

In sum, the dose-response 3-arm design has the advantages of allowing more insightful and rigorous inferences about causal effects of the mAb and greater resolution of correlates of protection, and allows addressing the additional question of whether a higher dose confers greater PE than a lower dose.

4.4 Sample size calculations for testing for overall PE (Primary objective 2)

For each cohort separately, the trial is designed to have 90% power to test

$H_0: PE \leq 0\%$ versus the alternative hypothesis $H_1: PE > 0\%$

if the level of overall pooled PE is 60%; the design fits the paradigm of an intermediate-sized phase 2b screening efficacy trial proposed for HIV-1 vaccine efficacy trials by Rida, Fleming et al [112]. The trial is powered for this level of efficacy separately for each cohort because (1) the mAb PE may vary by route of transmission/population and it is of interest to learn the answer in each cohort/setting; and (2) pooling the data from the two cohorts strengthens the assessment of correlates of protection, which, as subgroup analysis, generally requires more data than the assessment of overall PE.

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing log-transformed cumulative incidences of HIV-1 infection by the Week 80 visit between randomized groups, in the presence of the sequential monitoring described below. Power is computed based on simulating a large number of efficacy trials under assumptions described below using the R package seqDesign.

4.4.1 Assumptions of the sample size calculations including sequential monitoring for PE

The following assumptions are made for the sample size calculations, common for the two cohorts unless otherwise noted:

- 10% annual dropout incidence in each of the three study groups
- 30 month uniform accrual with halved accrual during the first three months
- visits every 4 weeks for HIV-1 diagnostic tests
- 3% annual HIV-1 incidence in the North/South American MSM + TG control group, against an assumed background of PrEP use
- 5.5% annual HIV-1 incidence in the sub-Saharan African women control group
- For each of the mAb treatment groups, average PE versus control within an 8-week infusion interval is assumed to be the same for each of the 10 infusion intervals
- Sequential monitoring of the mAb groups versus control to stop early for:
 - Potential harm (elevated rate of HIV-1 infection in each mAb group compared to control based on continuous monitoring after each infection and 1-sided monitoring adjusted 90% confidence interval [for PE10 or PE30] lying below 0%)
 - Non-efficacy [Establish that PE (pooled over the mAb groups) $\leq$ 40% based on a 95% nominal confidence interval lying below 40%]
 - High efficacy [Establish that PE (pooled over the mAb groups) $>$ 70% based on a 95% nominal confidence interval lying above 70%]

The non-efficacy monitoring and high efficacy monitoring are performed for the two mAb groups pooled versus the control group, such that the stopping guideline applies to the two groups pooled, and the guideline does not apply for stopping only one of the mAb groups. In contrast, the potential harm monitoring is performed separately for each of the two mAb groups.

The sequential monitoring of PE does not use critical values adjusted for the number of analyses because the levels of PE used in the guideline are far away from the design alternative of 60%, such that an adjustment would have minimal impact on the results.

Justification for the incidence assumptions is provided in Section 4.4.6.

We also show power calculations allowing for lower levels of HIV-1 incidence or higher levels of dropout. In particular, we show power calculations assuming 2% annual HIV-1 incidence in the North/South American MSM + TG control group and 4% annual HIV-1 incidence in the sub-Saharan African women control group, which would account for lower than expected incidence rates due to increased PrEP usage. Similarly, power calculations based on 15% annual dropout incidence are also considered.

4.4.2 Power curves and operating characteristics of the design (Primary objective 2)

Required sample sizes to achieve 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of PE are determined based on 1-sided 0.025 level Wald tests as described above. The power calculations are repeated for a range of sample sizes to determine the required sample size to achieve 90% power as reported in Figure 4-1 and Figure 4-2. These power calculations are conducted using the open source R package seqDesign developed by the protocol statisticians [113], which computes power based on simulating many thousands of efficacy trials, applying the sequential monitoring procedures to each trial, and computing power as the fraction of the trials where the 1-sided 0.025-level Wald test rejects the null hypothesis. The calculations are based on a large number of simulated vaccine efficacy trials.

Figure 4-1 shows the sample size per group in the three treatment groups required to have 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of $PE = PE_{10} = PE_{30}$ and the North/South American MSM + TG cohort. The results show that about $N = 2300$ total participants are needed to achieve 90% power to detect $PE = 60\%$; the sample size $N = 2400$ total participants (800 per arm) is selected to build in a provision of robustness to the control group annual incidence being lower than 3.0%.

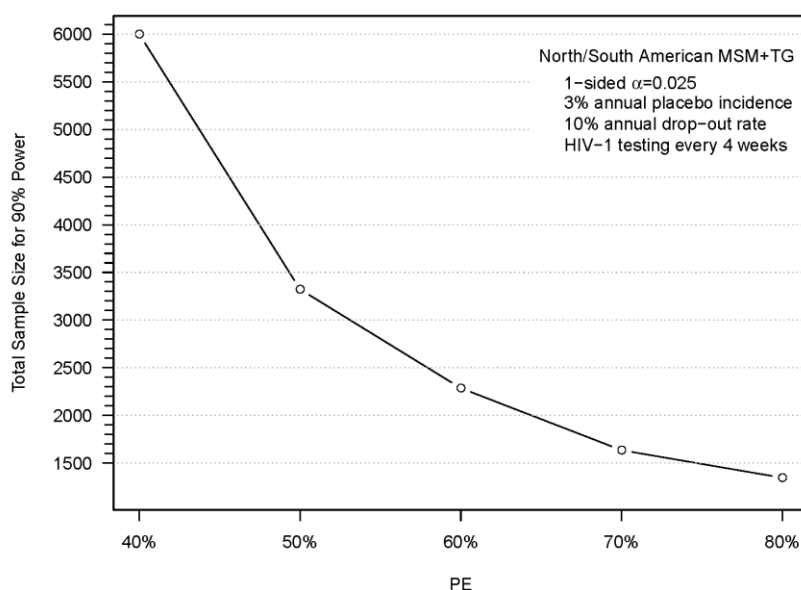


Figure 4-1 For the North/South American MSM + TG cohort, the total sample size for 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

Figure 4-2 shows the parallel results as Figure 4-1 for the sub-Saharan African women cohort. The results show that between $N = 1200$ and $N = 1300$ total participants are needed to achieve 90% power to detect $PE = 60\%$; the sample size $N = 1500$ total participants (500 per arm) is selected to build in a provision of robustness to the control group annual incidence being lower than 5.5%

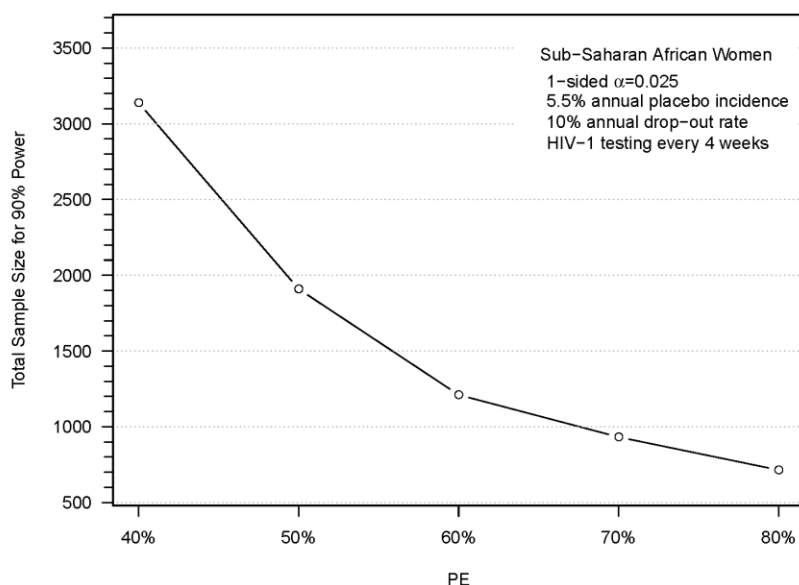


Figure 4-2 For the sub-Saharan African women cohort, the total sample size for 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

Table 4-1 shows power available to reject the null hypothesis under different levels of true PE, for each cohort.

Table 4-1 Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for each of the two cohorts under different effect sizes $PE = PE_{10} = PE_{30}$

	Unconditional Power ($\times 100$)	
	North/South American MSM+TG	Sub-Saharan African Women
0%	3.2	2.5
10%	7.9	6.6
20%	18.9	16.7
30%	34.3	39.3
40%	57.3	61.9
50%	81.4	83.14
60%	94.6	95.9
70%	99.1	99.8
80%	>99.9	>99.9

4.4.3 Additional operating characteristics of the design for assessing primary objective 2

For the selected total sample sizes ($N = 2400$ and $N = 1500$), Figure 4-3 and Figure 4-4 show the power curves for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for a range of fixed values of the pooled PE. The power for rejecting H_0 when the HIV-1 incidence rate is lower than projected or dropout rate is higher than projected are included in each figure.

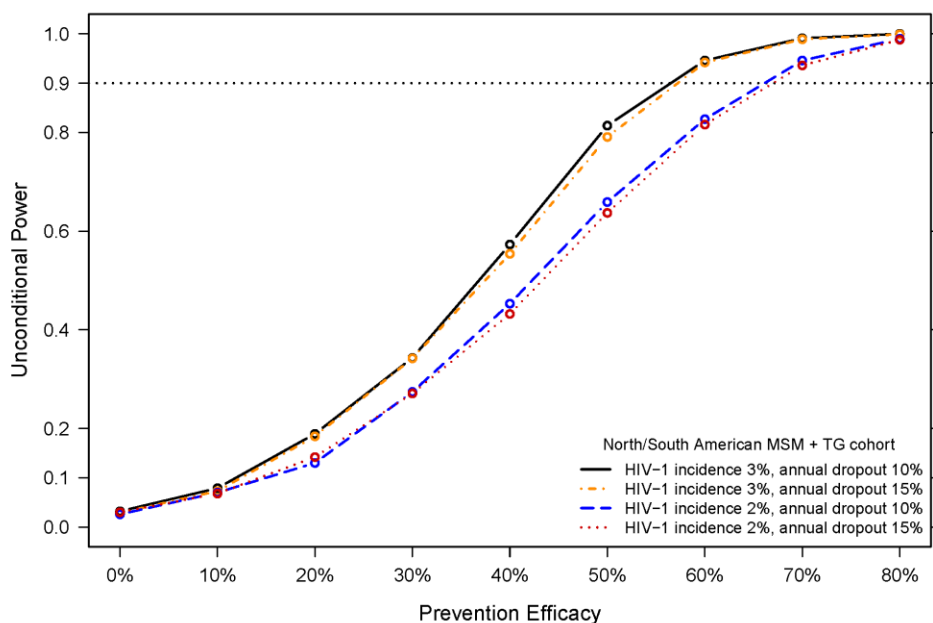


Figure 4-3 For the North/South American MSM + TG cohort and pooled mAb treatments, the power for rejecting H0: $PE \leq 0\%$ in favor of pooled prevention efficacy of level PE based on primary assumptions for HIV-1 incidence rate and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

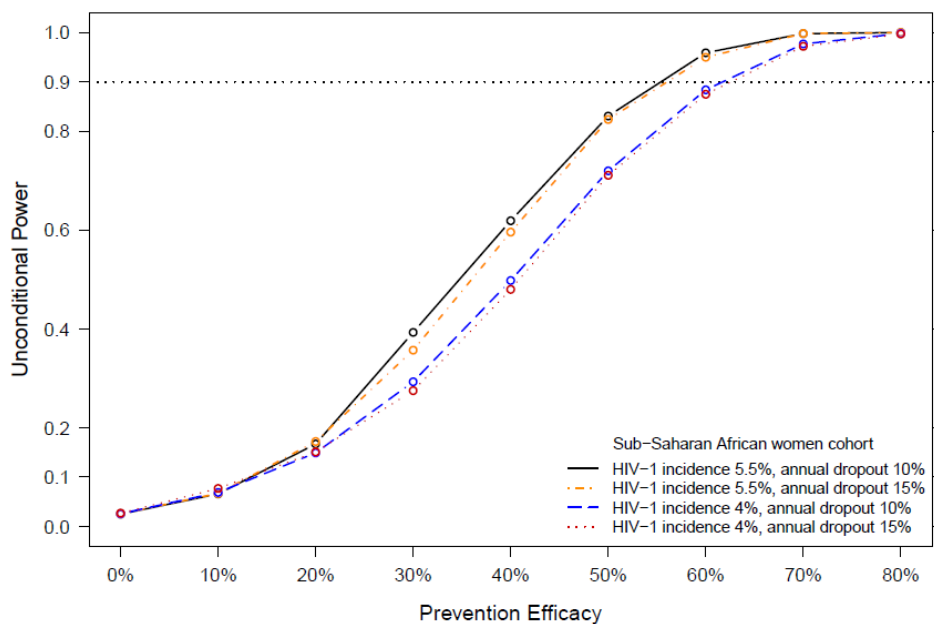


Figure 4-4 For the sub-Saharan African women cohort and pooled mAb treatments, the power for rejecting H0: $PE \leq 0\%$ in favor of pooled prevention efficacy of level PE based on primary assumptions for HIV-1 incidence rate and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.4.4 Additional operating characteristics of the primary analysis accounting for the sequential monitoring

For the selected total sample sizes ($N = 2400$ and $N = 1500$), Figure 4-5 and Figure 4-6 show probabilities of reaching each possible trial monitoring outcome, pooling over the two mAb treatments (under the primary assumptions about HIV-1 incidence and dropout rates). More specifically, the monitoring outcomes include potential harm, non-efficacy, and high efficacy. Table 4-2 and Table 4-3 provide the same information in tabular form. In addition, the figures and tables show unconditional power in the primary analysis to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$.

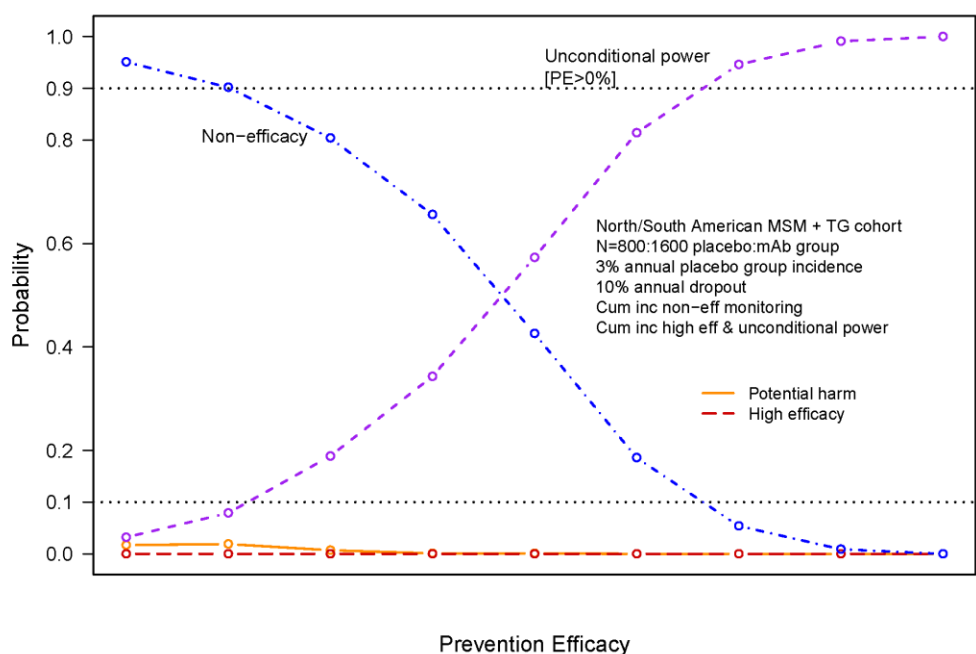


Figure 4-5 [North/South American MSM + TG cohort] Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$, pooling over the two mAb groups

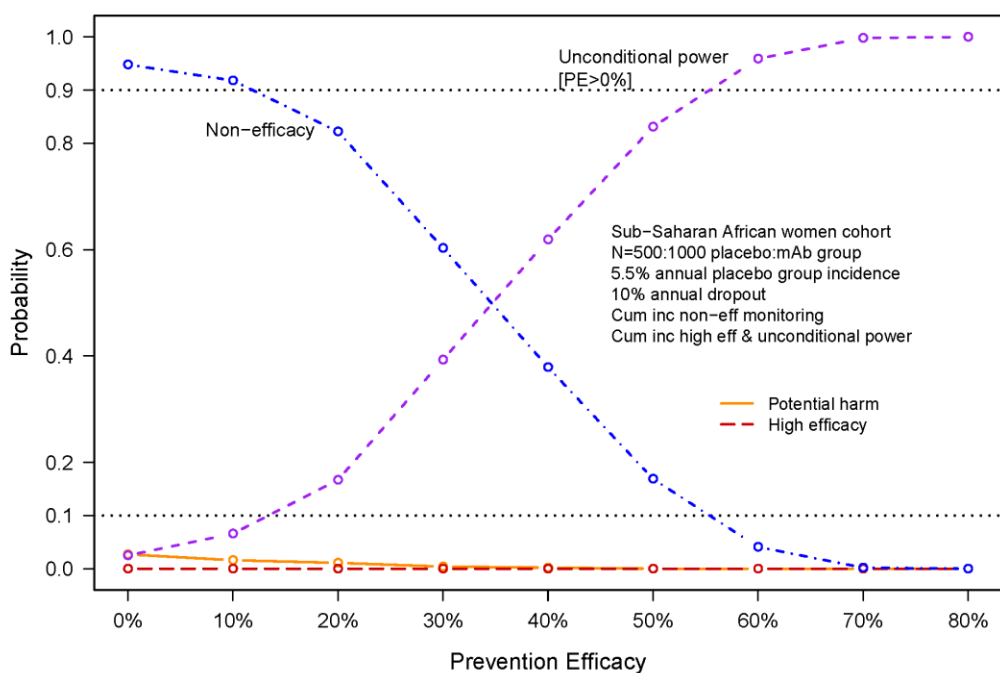


Figure 4-6 [Sub-Saharan African women cohort] Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups

Table 4-2 [North/South American MSM + TG cohort] Probabilities (x 100) of reaching each possible trial monitoring outcome, and unconditional power (x 100) to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups

PE	HR	Weed Out at Interim Analysis			Unconditional Power PE > 0%
		Potential Harm PE < 0%	Non-Efficacy PE < 40%	High Efficacy PE > 70%	
	3.0	80.3	19.7	0.0	0.0
	0.5	67.3	32.7	0.0	0.0
	2.0	43.7	56.3	0.0	0.0
	1.5	20.4	79.6	0.0	0.0
0%	1.0	1.7	95.1	0.0	3.2
10%	0.9	1.9	90.2	0.0	7.9
20%	0.8	0.7	80.4	0.0	18.9
30%	0.7	0.1	65.6	0.0	34.3
40%	0.6	0.1	42.6	0.0	57.3
50%	0.5	0.0	18.6	0.0	81.4
60%	0.4	0.0	5.4	0.0	94.6
70%	0.3	0.0	0.9	0.0	99.1
80%	0.2	0.0	0.0	0.0	100.0

North/South American MSM+TG cohort
N = 800:1600 Control:mAb group
3% annual incidence in the Control group
10% annual dropout
Cumulative incidence-based non-efficacy monitoring
Cumulative incidence-based high-efficacy monitoring
Cumulative incidence-based unconditional power

Table 4-3 [Sub-Saharan African women cohort] Probabilities (x 100) of reaching each possible trial monitoring outcome, and unconditional power (x 100) to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups

PE	HR	Weed Out at Interim Analysis			Unconditional Power PE > 0%
		Potential Harm PE < 0%	Non-Efficacy PE < 40%	High Efficacy PE > 70%	
	3.0	82.0	18.0	0.0	0.0
	0.5	68.2	31.8	0.0	0.0
	2.0	43.8	56.2	0.0	0.0
	1.5	19.8	80.2	0.0	0.0
0%	1.0	2.7	94.8	0.0	2.5
10%	0.9	1.6	91.8	0.0	6.6
20%	0.8	1.1	82.2	0.0	16.7
30%	0.7	0.4	60.3	0.0	39.3
40%	0.6	0.2	37.9	0.0	61.9
50%	0.5	0.0	16.9	0.0	83.1
60%	0.4	0.0	4.1	0.0	95.9
70%	0.3	0.0	0.2	0.0	99.8
80%	0.2	0.0	0.0	0.0	100.0

Sub-Saharan African women cohort

N = 500:1000 Control:mAb group

5.5% annual incidence in the Control group

10% annual dropout

Cumulative incidence-based non-efficacy monitoring

Cumulative incidence-based high-efficacy monitoring

Cumulative incidence-based unconditional power

For each cohort, Table 4-4 shows the numbers of HIV-1 infection endpoints during the trial expected under the null hypothesis scenario PE = PE10 = PE30 = 0% and under the design alternative hypothesis scenario PE = PE10 = PE30 = 60%. The calculations show that 33 (37) HIV-1 infection endpoints are expected in the control group for the North/South American MSM + TG cohort (sub-Saharan African women cohort). Under the design alternatives PE10 = PE30 = 60%, 27 (31) total HIV-1 infection endpoints are expected pooled over the two mAb groups for the North/South American MSM + TG cohort (sub-Saharan African women cohort). Therefore, in the design alternatives scenario, 58 total breakthrough HIV-1 infections in the two mAb recipient groups are expected to contribute to the cohort-pooled correlates of protection analysis.

Table 4-4 Cumulative number of HIV-1 infection endpoints over 80 weeks of follow-up for the North/South American MSM + TG cohort (N=2400) and the sub-Saharan African women cohort (N = 1500) under the null hypothesis scenario PE10 = PE30 = 0% and under the design alternative hypothesis scenario PE = PE10 = PE30 = 60%. Medians are computed based on simulating a large number of efficacy trials.

Cohort	PE10 = PE30	Weeks since first person in	Median number of control endpoints	Median number of pooled mAb group endpoints
North/South American MSM + TG	0%	0	0	0
	0%	26	1	2
	0%	52	6	12
	0%	78	15	30
	0%	104	25	49
	0%	130	30	60
	0%	156	32	64
	0%	158	32	64
	60%	0	0	0
	60%	26	1	1
	60%	52	6	5
	60%	78	15	12
	60%	104	25	20
	60%	130	31	25
	60%	156	33	27
	60%	158	33	27
Sub-Saharan African women	0%	0	0	0
	0%	26	1	3
	0%	52	7	14
	0%	78	17	34
	0%	104	28	56
	0%	130	35	68
	0%	156	37	72
	0%	158	37	72
	60%	0	0	0
	60%	26	1	1
	60%	52	7	6
	60%	78	17	14
	60%	104	28	23
	60%	130	35	28
	60%	156	37	31
	60%	158	37	31

4.4.5 Power curves for secondary hypothesis tests about PE in each mAb group

Figure 4-7 and Figure 4-8 show unconditional power in each cohort to reject the null hypothesis $H_0: PE_{10} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{10} > 0\%$ (or, equivalently, the null hypothesis $H_0: PE_{30} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{30} > 0\%$), where PE10 and PE30 measure prevention efficacy in each mAb group separately.

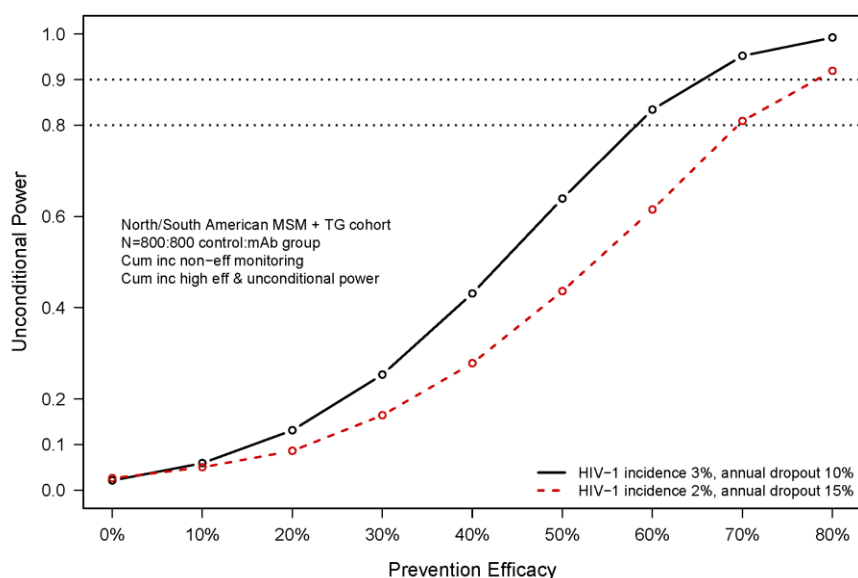


Figure 4-7 For the North/South American MSM + TG cohort and each mAb group separately, power for rejecting $H_0: PE_{10} \leq 0\%$ in favor of $H_1: PE_{10} > 0\%$ (or $H_0: PE_{30} \leq 0\%$ in favor of $H_1: PE_{30} > 0\%$) based on primary assumptions about HIV-1 incidence rate and dropout rate. A power curve is also shown for a scenario with a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

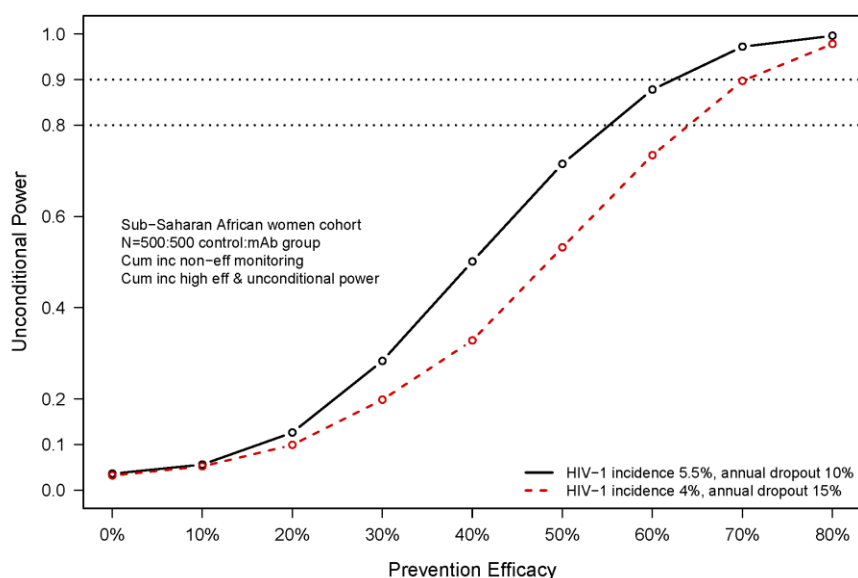


Figure 4-8 For the sub-Saharan African women cohort and each mAb group separately, power for rejecting $H_0: PE_{10} \leq 0\%$ in favor of $H_1: PE_{10} > 0\%$ (or $H_0: PE_{30} \leq 0\%$ in favor of $H_1: PE_{30} > 0\%$) based on primary assumptions about HIV-1 incidence rate and dropout rate. A power curve is also shown for a scenario with a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

4.4.6 Rationale for the HIV-1 incidence assumptions

The assumption of 3% annual HIV-1 incidence in the North/South American MSM + TG control group accommodates background PrEP use by assuming incidence is decreased

by two parameters: (1) the fraction of person-years at-risk during which PrEP is used; and (2) the level of efficacy of PrEP during PrEP use. Figure 4-9 shows the annual HIV-1 incidence in the control group as a function of these two factors, for a scenario where the annual HIV-1 incidence is 4% in the absence of any PrEP use. Based on HVTN 505 data (US participants only) through September 30, 2014, the annual HIV-1 incidence in the control group was 2.0% (95% CI 1.5%—2.7%) and in the vaccine and control groups pooled was 2.1% (95% CI 1.5%—2.8%). From HVTN 505, based upon case report form collection of PEP/PrEP med usage and responses to questions regarding usage posed on the ‘anonymous’ (to the site) ACASI questionnaire through June 1, 2014, 5% of participants reported ever using PrEP. Therefore in HVTN 505 the amount of person-years at risk during periods of PrEP use was likely well below 5%, and therefore the 2.1% annual incidence is a reasonable assumption for the baseline rate in US MSM + TG without PrEP. Thus, the assumption of 3% annual incidence requires that a substantial fraction of the enrolled participants are from South American sites where the HIV-1 incidence is anticipated to be higher than 3%. In particular, assuming 1.6% annual control incidence in the US (accounting for substantially greater PrEP use than in HVTN 505, about 30% of person-years at risk during PrEP use and 80% PrEP efficacy during use) and assuming 5% annual control incidence in South American participants [6], 41% of participants enrolled at South American sites would yield the assumed 3% annual control incidence rate.

The assumption of 5.5% annual HIV-1 incidence for the control group of sub-Saharan African women is based on recent data directly measuring HIV-1 incidence in women at several African sites [69-72,85]. The overall annual incidence rate in the VOICE study was 5.7%, which pools over all intervention groups given the similar incidence rates and the lack of significant differences. Although the annual incidence rate of female control recipients in the Phambili study, at 3.2%, was lower than the assumed rate of 5.5%, the Fem-Prep study had an annual incidence rate of 5% in the control group and the CAPRISA 004 study had an annual incidence rate of 9.1% in the control gel arm.

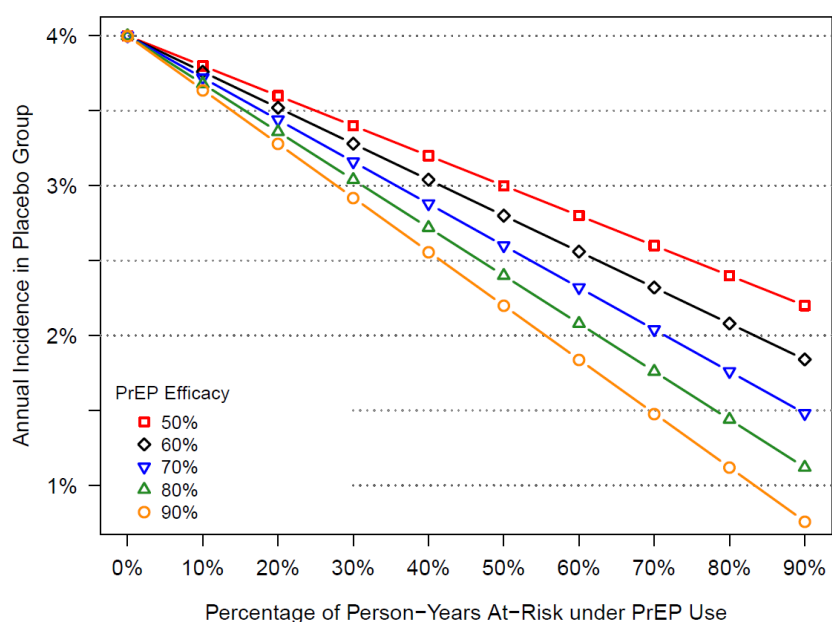


Figure 4-9 Annual HIV-1 incidence in the North/South American MSM + TG control group assuming 4% annual HIV-1 incidence in the hypothetical scenario of no PrEP use, under different levels of PrEP use and levels of PrEP efficacy

Based on a synthesis of the above-cited references using control arms or active arms in trials that showed no efficacy, we assume that the background annual incidence of HIV-1 in sub-Saharan African women in the absence of any PrEP use is 6.4%. It is difficult to predict the degree of PrEP use that will occur in sub-Saharan African women. Given that currently PrEP is not licensed for sub-Saharan African women and is currently seldom used outside of controlled clinical trials, for the protocol we assume that no more than 15% of the PYRs at-risk are during PrEP use periods. This assumption leads to the 5.5% incidence assumption after accounting for the 15% PYRs at risk with a supposed 90% PrEP efficacy during PrEP use.

Higher than expected use of PrEP in either study group will be reflected in lower than expected annual incidence rates as shown in Figure 4-9. As shown in Figure 4-3 and Figure 4-4, the trial would still provide enough statistical information to be powered to detect highly relevant prevention efficacy effect sizes if annual incidence rates are lower than we have estimated here due to higher than expected use of PrEP.

4.5 Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group

Table 4-5 reports power calculations for comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups, for each cohort separately and pooling across the two cohorts. The calculations assume the scenarios for true values of PE10 and PE30 indicated in the first two columns of the table. The results show that the study is well-powered to detect moderate differences pooling over the two cohorts and to detect only large differences within each individual cohort (right-most column). In contrast, the study has high power to correctly select the best mAb dose group within each cohort given moderate efficacy differences. Specifically, if the true PE30 is moderately greater than the true PE10, then there is high probability that the estimated PE30 would be greater than the estimated PE10, such that the 30 mg/kg mAb dose group would be selected.

Table 4-5 Statistical power for comparing the 10 versus 30 mg/kg mAb groups: Power to select the best mAb group and power to correctly select the best mAb group, for each cohort separately and pooled over the cohorts

Cohort	PE10	PE30	Power to Select Best mAb Dose Group [§]	Power to Detect PE10 Different from PE30 [#]
North/South American MSM+TG	20%	60%	79.1	45.3
	30%	60%	77.3	30.6
	40%	60%	72.4	16.4
	30%	70%	89.1	54.3
	50%	85%	95.7	54.3
Sub-Saharan African women	20%	60%	84.1	53.4
	30%	60%	83.3	32.7
	40%	60%	77.2	19.3
	30%	70%	93.5	62.2
	50%	85%	98.1	60.3
Cohorts pooled	20%	60%	98.7	86.4
	30%	60%	98.3	66.0
	40%	60%	94.3	37.6
	30%	70%	>99.9	91.5
	50%	85%	>99.9	92.4

[§] Probability that the mAb dose group that is truly better (the 30 mg/kg dose group in the scenarios considered in the table) is correctly selected based on the point estimate for PE30 exceeding that for PE10. Specifically, correct selection entails that the estimated PE30 is greater than the estimated PE10 and PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

[#] Cumulative hazard-based Wald tests comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. Rejection of the null hypothesis requires that PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

4.6 Sample size calculations for safety

We consider the statistical power of Fisher's exact test to detect a higher rate of SAEs in a mAb group (Group 1 or 2 with $n = 800$ participants or Group 4 or 5 with $n = 500$) versus the control group from the same cohort (either Group 3 with $n = 800$ in the US + South American MSM + TG cohort or Group 6 with $n = 500$ in the sub-Saharan African women cohort). Based on HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE. The tests use a 2-sided α -level of 0.05. This level does not correct for the 4 comparisons; however this is appropriate because it is desirable to maximize power to detect a safety problem. For the safety calculations, we assume no missing data as almost all participants will have some follow-up data for safety.

To describe the precision of the study to characterize differences in SAE rates between groups, Table 4-6 shows 2-sided 95% CIs for different levels of observed differences (mAb group-control) of event rates between a mAb group of size $n_1 = 800$ (or the combined mAb groups $n_2 = 1600$) and a control group of size $n_0 = 800$, representing the sample sizes for the North/South American MSM + TG cohort. For example, an observed rate difference of 6% between the combined mAb groups and control group will lie between 3.5% and 8.7% with 95% confidence, when the observed event rate in the control group is 4%. Table 4-7 shows 95% CIs for differences based on the sample sizes for the Sub-Saharan African Women cohort.

Table 4-6 Two-sided 95% confidence intervals for different observed event rate differences of safety endpoints between the mAb recipient and control groups for North/South American MSM + TG cohort*

Observed event rate in controls ($n_0 = 800$)	Observed event rate in single mAb group ($n_1 = 800$)	Observed event rate in combined mAb groups ($n_2 = 1600$)	Rate difference (mAb group – control)	95 % CI ($n_1 = 800$)	95% CI ($n_2 = 1600$)
0/800 = 0%	0/800 = 0%	0/1600 = 0%	0%	(-0.0115, 0.0163)	(-0.0103, 0.0095)
	16/800 = 2%	32/1600 = 2%	2%	(0.0051, 0.0391)	(0.0076, 0.0349)
	32/800 = 4%	64/1600 = 4%	4%	(0.0225, 0.0614)	(0.0260, 0.0563)
	80/800 = 10%	160/1600 = 10%	10%	(0.0767, 0.1265)	(0.0822, 0.1197)
	160/800 = 20%	320/1600 = 20%	20%	(0.1704, 0.2319)	(0.1780, 0.2233)
16/800 = 2%	0/800 = 0%	0/1600 = 0%	-2%	(-0.0391, -0.0051)	(-0.0356, -0.0089)
	16/800 = 2%	32/1600 = 2%	0%	(-0.0211, 0.0254)	(-0.0186, 0.0213)
	32/800 = 4%	64/1600 = 4%	2%	(-0.0030, 0.0470)	(0.0003, 0.0422)
	80/800 = 10%	160/1600 = 10%	8%	(0.0524, 0.1109)	(0.0575, 0.1046)
	160/800 = 20%	320/1600 = 20%	18%	(0.1471, 0.2153)	(0.1542, 0.2073)
32/800 = 4%	0/800 = 0%	0/1600 = 0%	-4%	(-0.0614, -0.0225)	(-0.0585, -0.0256)
	16/800 = 2%	32/1600 = 2%	-2 %	(-0.0470, 0.0030)	(-0.0424, -0.0019)
	32/800 = 4%	64/1600 = 4%	0%	(-0.0260, 0.0300)	(-0.0228, 0.0253)
	80/800 = 10%	160/1600 = 10%	6%	(0.0299, 0.0935)	(0.0348, 0.0873)
	160/800 = 20%	320/1600 = 20%	16%	(0.1250, 0.1973)	(0.1318, 0.1897)

*95% confidence intervals are computed using the method of Berger and Boos [114]. Entries are bolded where significantly more events are observed among mAb recipients than among control recipients based on the 95% confidence interval.

Table 4-7 Two-sided 95% confidence intervals for different observed event rate differences of safety endpoints between the mAb recipient and control groups for sub-Saharan African Women cohort*

Observed event rate in controls (n0 = 500)	Observed event rate in single mAb group (n1 = 500)	Observed event rate in combined mAb groups (n1 = 1000)	Rate difference (mAb group – control)	95 % CI (n1 = 500)	95% CI (n1 = 1000)
0/500 = 0%	0/500 = 0%	0/1000 = 0%	0%	(-0.0183, 0.0258)	(-0.0164, 0.0151)
	10/500 = 2%	20/1000 = 2%	2%	(-0.0018, 0.0486)	(0.0015, 0.0426)
	20/500 = 4%	40/1000 = 4%	4%	(0.0153, 0.0710)	(0.0197, 0.0641)
	50/500 = 10%	100/1000 = 10%	10%	(0.0686, 0.1365)	(0.0754, 0.1276)
	100/500 = 20%	200/1000 = 20%	20%	(0.1611, 0.2425)	(0.1706, 0.2316)
10/500 = 2%	0/500 = 0%	0/1000 = 0%	-2%	(-0.0486, 0.0018)	(-0.0426, -0.0046)
	10/500 = 2%	20/1000 = 2%	0%	(-0.0293, 0.0361)	(-0.0259, 0.0300)
	20/500 = 4%	40/1000 = 4%	2%	(-0.0115, 0.0578)	(-0.0072, 0.0511)
	50/500 = 10%	100/1000 = 10%	8%	(0.0431, 0.1221)	(0.0496, 0.1136)
	100/500 = 20%	200/1000 = 20%	18%	(0.1368, 0.2268)	(0.1457, 0.2166)
20/500 = 4%	0/500 = 0%	0/1000 = 0%	-4%	(-0.0710, -0.0153)	(-0.0659, -0.0209)
	10/500 = 2%	20/1000 = 2%	-2 %	(-0.0578, 0.0115)	(-0.0509, 0.0041)
	20/500 = 4%	40/1000 = 4%	0%	(-0.0352, 0.0415)	(-0.0309, 0.0348)
	50/500 = 10%	100/1000 = 10%	6%	(0.0199, 0.1052)	(0.0262, 0.0970)
	100/500 = 20%	200/1000 = 20%	16%	(0.1142, 0.2094)	(0.1227, 0.1996)

*95% confidence intervals are computed using the method of Berger and Boos [114]. Entries are bolded where significantly more events are observed among mAb recipients than among control recipients based on the 95% confidence interval.

Figure 4-10 shows the power to detect an elevated SAE rate as a function of the true rate in the mAb group under consideration.

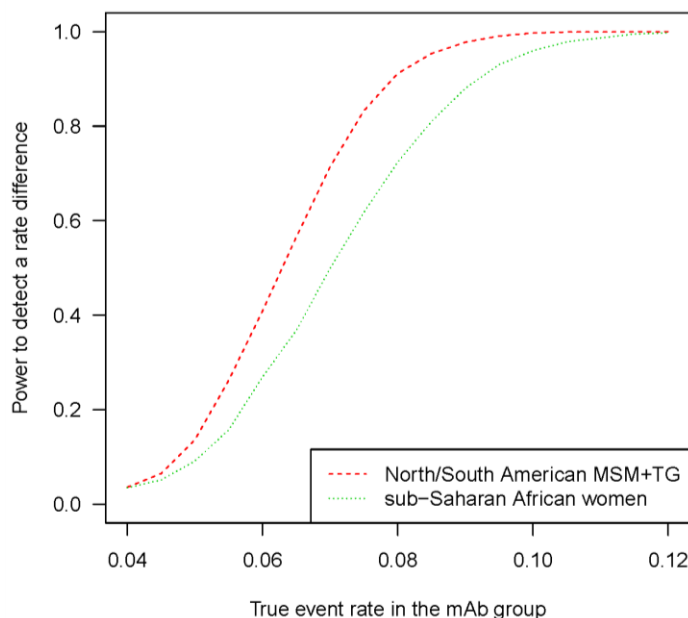


Figure 4-10 Power to detect a greater SAE rate in a mAb group versus the control group for each cohort given a 4% SAE rate in the control group

Figure 4-10 shows that there is 80% power to detect a higher SAE rate in a mAb arm if the true rate is 7.4% and 90% power if the true rate is 7.9% for the North/South American MSM + TG cohort and there is 80% power if the true rate is 8.4% and 90% power if the true rate is 9.2% for the Sub-Saharan African women cohort.

4.7 Monitoring of the trial

Trial monitoring will be conducted independently for each cohort.

4.7.1 Role of the Data Safety Monitoring Board (DSMB)

The study DSMB will review unblinded study data at interim analyses performed approximately every 4 months to evaluate safety, integrity, and efficacy of the ongoing trial. Following each DSMB meeting, the DSMB reports to the Oversight Committee a summary of the trial review, which may include recommendations to modify or terminate the trial for one or both study cohorts. The DSMB is guided by a trial monitoring plan, and reviews and approves the monitoring plan before the trial initiates.

4.7.1.1 Sequential monitoring for potential harm, efficacy futility, and high efficacy

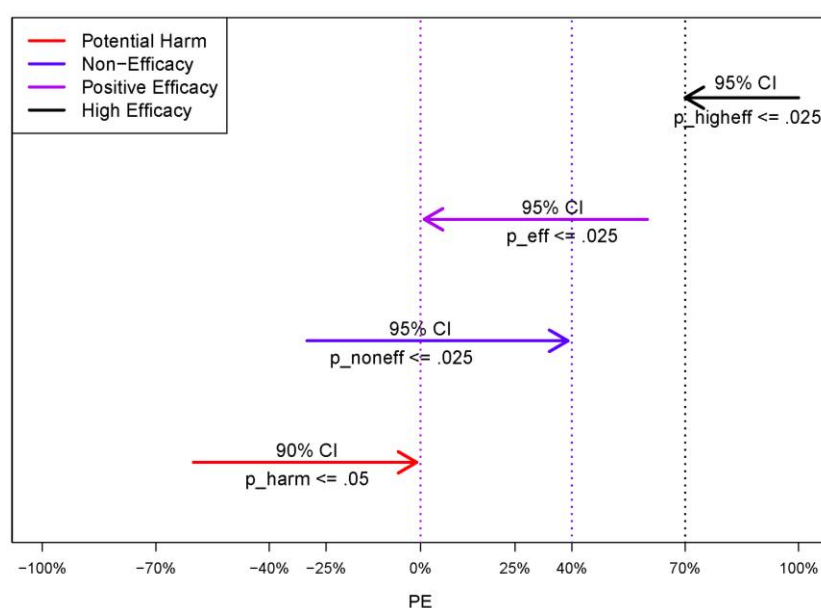
The trial uses sequential monitoring of the mAb groups versus control to stop early for:

- Potential harm [Establish an elevated rate of HIV-1 infection in one of the mAb groups compared to control based on continuous monitoring after each infection and 1-sided monitoring adjusted 90% confidence interval (for PE10 or PE30) lying below 0%]
- Non-efficacy [Establish that PE (pooled over the mAb groups) $\leq$ 40% based on a 95% nominal confidence interval lying below 40%]
- High efficacy [Establish that PE (pooled over the mAb groups) $>$ 70% based on a 95% nominal confidence interval lying above 70%]

The sequential monitoring is based on 95% confidence intervals in order that the result of the study that would be reported would convey evidence supporting the conclusion of potential harm, efficacy futility, or high efficacy. Freidlin, Korn, and Gray [78] discuss a rationale for this approach to efficacy futility monitoring. The sequential monitoring plan for each cohort is summarized in Table 4-8 and Figure 4-11.

Table 4-8 Summary of sequential monitoring of PE for each study cohort

Monitoring Type	Hypotheses	Testing Approach	Size/Power	Monitoring Plan	Number of Interim Analyses
Potential Harm	H0: PE $\geq$ 0% vs H1: PE < 0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the mAb	1-sided $\alpha = 0.05$	Constant p-value cut-off controlling the FWER at $\alpha = 0.05$	After every infection from 10 th until first non-efficacy analysis
Non-Efficacy	H0: PE $\geq$ 40% vs H1: PE < 40%	Wald test	1-sided $\alpha = 0.025$	Nominal 95% CI supplemented with conditional power	4-monthly starting when H0 may be rejected with Est. PE = 0%
High Efficacy	H0: PE $\leq$ 70% vs H1: PE > 70%	Wald test	1-sided $\alpha = 0.025$	Nominal 95% CI	4-monthly starting at the same time as for non-efficacy

**Figure 4-11 Stopping boundaries for the sequential monitoring of each study cohort**

Details of the sequential monitoring plan will be provided in a separate trial monitoring plan. The sequential monitoring is closely related to what was done for the HVTN 505 HIV-1 vaccine efficacy trial [115] and to what is planned for the HVTN 701 phase 2b HIV-1 vaccine efficacy trial (background discussion in [79]).

4.7.2 Feasibility check and guideline for continuing enrollment as planned

In addition to the sequential monitoring of PE, feasibility monitoring is done for the first 240 enrolled participants. This feasibility monitoring is based on the first four 8-week intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of participants attends clinical visits and receives the infusions per the protocol. The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) and an adequately high rate of visit attendance, which corresponds to adherence to receipt of infusions. Additional details will be provided in the trial monitoring plan.

The feasibility monitoring based on the first 240 enrolled participants will use the following guideline for continuing enrollment as planned: continued participation by the Week 32 visit pooled over the 6 groups is greater than 80%.

If the blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is warranted.

4.7.3 Monitoring for operational futility

For each cohort, define the Target Number of Infections to be the number of diagnosed HIV-1 infections after Week 0 and by the Week 80 visit such that the trial has approximately 90% power to reject $H_0: PE \leq 0\%$ if $PE = 60\%$ in the primary analysis. This number is 60, calculated based on the simulated trials described above. Define the Time to the Target Number of Infections (TTNI) to be the number of months from the time of the first enrolled participant until the 60th diagnosed HIV-1 infection after Week 0 and by Week 80. The objective of the operational futility monitoring, conducted for each cohort, is to provide to the DSMB periodic projections of the estimated distribution of the TTNI. If the probability of reaching the TTNI within a specified time frame is too low, then a guideline would be met for recommending completing the trial for a cohort based on the inability to answer the primary PE question in a timely manner.

The projections of the TTNI will be provided to the DSMB at each 4-monthly DSMB meeting starting at the meeting taking place at approximately 8 months after the first volunteer is enrolled. This calculation will use the observed recruitment, HIV-1 incidence, and retention rates. The sample size calculations assume 30 months of enrollment and 80 weeks of total follow-up per participant for monitoring for primary HIV-1 infection endpoints, constituting $30 + 18.46$ months = 48.46 months. If the projected TTNI for a cohort reliably exceeds 48.46 months after trial opening, then the DSMB should consider maneuvers to reduce this waiting time. In particular, if continued recruitment could reduce the projected TTNI by more than 3 months, sites (or selected sites with relatively high recruitment rates) would be expected to extend recruitment for up to 6 months. If the projected TTNI reliably exceeds 60 months (5 years) after appropriate attempted remediation, then the DSMB should consider recommending termination of the trial for the cohort under consideration. In the event that the trial is terminated for both cohorts, then at that time the final analysis would be performed.

Calculation of the projected TTNI at an interim analysis

The method for projecting the TTNI for each cohort is based on the following approach to simulating efficacy trials. A similar process was used for HVTN 505. The trial is modeled as a combination of three processes — enrollment, dropout, and HIV-1 infection — and a large number of trials is simulated. The three processes are assumed independent and their distributions are taken to be Poisson, exponential, and exponential, respectively. Data are generated at the level of the individual participant, such that for each participant we obtain an enrollment time, an (underlying true) infection time, and a dropout time. Only the minimum of the infection and dropout times is observable, and the average value for this minimum is beyond the duration of the trial, such that neither event will be observed for most participants. The parameters for the enrollment, infection, and dropout processes are chosen to match our pre-trial assumptions regarding these rates:

- Enrollment rate: 9.72 participants per week in weeks 1-13; 19.43 participants per week in weeks 14-130 [MSM+TG cohort]; 6.07 participants per week in weeks 1-13; 12.15 participants per week in weeks 14-130 [sub-Saharan African women cohort]
- Dropout rate: 0.10 dropouts/person-year [both cohorts]
- Infection rate: 0.03 infections/person-year [MSM+TG cohort]; 0.055 infections/person-year [sub-Saharan African women cohort]

The first step in simulating each trial is to enroll a certain number of participants per week according to a random draw from a Poisson distribution with rate parameter as listed above. Enrollment continues week-by-week until a total of 2400 or 1500 participants is reached. Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. Following enrollment, the infection and dropout times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider dropout events to have occurred at the dropout time (in days) that was generated (assuming it was less than the infection time). For participants who become HIV-1 infected, we record their time of diagnosis as the time of the first study visit following the true infection time. It is this time of diagnosis that we observe for infected participants.

Once all participants have had their enrollment and infection/dropout times generated and (if necessary) infection diagnosis time determined, we can then obtain the TTNI for the simulated trial. For participants with HIV-1 infection diagnosis, we add their enrollment and infection diagnosis times together to obtain diagnosis times that are relative to the beginning of the study (in calendar time) rather than in relation to their own enrollment times. Finally, we order these participants by these new infection diagnosis times, from smallest to largest, and identify the 60th one from the beginning. The TTNI is this 60th infection diagnosis time after Week 0 by the Week 80 visit.

A modification of the above procedure for simulating the efficacy trial for a cohort is used for predicting the TTNI at a given interim analysis. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on pre-trial assumptions. In particular:

- Enrollment rate: Estimated based on the rate observed thus far in the study
- Dropout rate: Estimated based on the rate observed thus far in the study
- Infection rate: Estimated based on a posterior distribution for the infection rate formed by combining the observed data with our prior belief about the infection rate based on the pre-trial assumptions

A new value for the infection rate is sampled from the posterior distribution for each simulated trial. The rationale for this approach is to help stabilize the infection rate early in the trial, when insufficient time will have passed to accrue many infections. If we were to rely solely on the observed infections, we might by chance obtain a very low rate, which would lead to an unrealistic prediction of the TTNI. The effect of the prior is highest early in the trial, when we have the least data, and is gradually reduced as more trial data accumulate. By the year 2 interim analysis, the prior has little effect. We use a

gamma distribution prior (which is conjugate to the exponential used for the infection rate), with parameters chosen so that the prior mean matches the pre-trial assumption for the infection rate and with information content approximately equivalent to what is expected in the first 12 months of the study.

At a given interim analysis, the TTNI is estimated based on simulating 100,000 trials using the above procedure, each of which yields a predicted TTNI. The projected TTNI is the median predicted TTNI over the 100,000 trials. As noted earlier, the guideline for declaring operational futility is that the projected TTNI lies reliably above 5 years. Our translation of this into practice is that we require that at least 75% of the 100,000 predicted TTNI values be greater than 5 years (ie, the probability that the true TTNI is greater than 5 years is at least 0.75).

The trial monitoring plan will include evaluation of the operating characteristics of the TTNI projection method.

Performance standards for quality of trial conduct

The protocol team and study investigators will have performance standards regarding the quality of trial conduct in addition to the HIV-1 infection diagnosis rate. In addition to projections of the distribution of the TTNI, at each interim analysis the DSMB is provided treatment-pooled plots of enrollment over calendar time. Kaplan-Meier estimates of treatment-pooled cumulative incidences of dropout, discontinuation of mAb infusions, and HIV-1 infection is also provided, together with Kaplan-Meier estimates of the cumulative incidence of “discontinued participation” that can occur due to dropout or to withdrawal from receipt of infusions. In addition, tables will be provided summarizing expected versus observed 4-weekly visit attendance rates and rates of received infusions among participants attending visits. All of these results will be provided for each cohort overall and by study site. The DSMB and the protocol team leadership will monitor whether the trial is achieving at least minimally acceptable levels regarding key performance standards.

Feasibility check

When the data are available for the feasibility check, this reported information will constitute the key results for the feasibility check. In particular, the rate of “continued participation,” used in the guideline of an 80% continuation rate, is determined from the cumulative incidence of “discontinued participation” described above. A separate report containing the results of the feasibility check will be shared with the protocol team leadership as well as with the DSMB.

4.8 Assessment of ARV drug use

Studies by the HPTN Laboratory Center have documented that off-study ARV drug use may not be disclosed to study staff [116-119]. Use of a high-throughput multi-drug assay will allow assessment of both use of TFV/FTC for PrEP (either off-study or provided in the study), as well as use of other ARVs that may impact study outcomes (eg, by lowering HIV incidence with a loss of study power). Because there are relatively few data describing patterns of ARV use in the relevant study populations and regions, and because patterns of ARV use among HIV-uninfected individuals may be regional [119]

and are likely to change over time, it is difficult to predict the prevalence or pattern of ARV drug use in the study cohort.

The ARV assay described in Section 9.6 will provide information on the prevalence of ARV drug use in the study population, as well as the type of ARVs used. Most likely, the analysis will begin with a comprehensive assessment of ARV use among all study participants at enrollment. ARV drug use may be stratified into three groups: (1) no ARVs detected, (2) TFV and/or FTC only detected (consistent with use of FTC/TDF for PrEP), and (3) one or more ARVs other than TFV and/or FTC detected. Note that in some cases, TFV and/or FTC may be detected along with other ARVs. The specific plan for selecting follow-up samples for testing will be defined at a later date (see statistical analysis plan [SAP]). This may include cross-sectional testing of the entire cohort, a random subset of the cohort, or samples from selected study sites. For individuals who acquire HIV infection during the study, samples may be tested from the first HIV-positive visit and selected prior study visits to assess ARV use. Samples from individuals who are not infected may be tested for comparison, to explore a potential impact of ARV use on PE of the study product. Data obtained using the ARV assay will also be compared to data collected from self-reported ARV use (eg, for PrEP, PEP, recreational use).

4.9 Randomization

The randomization sequence will be obtained by computer-generated random numbers and provided to each CRS through a Web-based randomization system. The randomization will be done in blocks to ensure balance across arms. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the SSP). Randomization will be stratified by study site.

4.10 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know this information in order to ensure proper trial conduct. Any discussion of study product assignment between pharmacy staff and any other CRS staff is prohibited.

When a participant leaves the trial prior to study completion, the participant will be told he or she must wait until all participants are unblinded to learn his or her treatment assignment.

Emergency unblinding decisions will be made by the site investigator. If time permits, the HVTN 703/HPTN 081 PSRT should be consulted before emergency unblinding occurs.

4.11 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many infusions they received. In the rare instance that a participant receives the wrong treatment at a specific infusion visit, the Statistical Analysis Plan will address how to analyze the participant's safety data. Analyses are modified intent-to-treat in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected.

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

4.11.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, efficacy, and markers of mAb characteristics for primary- and secondary-objective analyses.

4.11.2 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

4.11.3 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first infusion, all participants will have received at least 1 infusion and therefore will provide some safety data.

4.11.3.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

4.11.3.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

4.11.3.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section 10.2.2) will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

4.11.3.4 Reasons for infusion discontinuation and early study termination

The number and percentage of participants who discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

4.11.4 Efficacy analysis

4.11.4.1 General approach

For the statistical analysis of prevention efficacy, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Given that all or almost all participants will receive the first infusion, the analyses are modified intention to treat (MITT), where all participants HIV-1 negative at entry receiving the initial infusion are included in the analysis, participants are analyzed according to their randomized treatment assignment, and participants retrospectively determined to be HIV-1 infected at entry based on treatment blinded procedures are excluded from the analysis. Additional analyses may be performed, limited to participants who received most or all infusions per protocol.

Cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms will be estimated by a transformation of Nelson-Aalen estimators [120] for the respective cumulative hazard functions of HIV-1 infection. PE parameters will be estimated by one minus the ratio (mAb/control group) of these cumulative incidence estimators. Point estimates and 95% Wald confidence intervals about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported. These procedures will be used to test the hypotheses listed in Section 4.2.

As a supportive analysis for the hypotheses listed in Section 4.2, targeted maximum likelihood estimation (tMLE) will be used to estimate cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms [121,122]. The Statistical Analysis Plan will describe the details of implementation of the tMLE estimators in an automated and objective fashion. PE parameters will be estimated by one

minus the ratio (mAb group/control) of these tMLE estimators. Point estimates and 95% Wald confidence intervals about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of HIV-1 infection over time, complementary secondary analyses will assess PE using Cox proportional hazards models and score tests for testing whether PE differs from zero. Goodness-of-fit diagnostics will be applied to assess veracity of the proportional hazards assumption. The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity of the primary analysis does not depend on the proportional hazards assumption.

4.11.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety or efficacy endpoint assessments.

4.11.6 Specific approach for assessing PE, PE10, PE30

Primary objective 2 is addressed based on comparing cumulative HIV-1 incidence between the group of participants assigned to receive the VRC01 mAb (at either dose pooling over the two doses) and the group of participants assigned to the control group, and secondarily between each individual mAb dose group and the control group. For each prevention efficacy parameter PE, PE10 and PE30, point and 95% confidence interval (CI) estimates will be reported, along with the 2-sided p-values for testing the respective null hypotheses (with 2-sided $p = 0.05$ the threshold for a significant effect).

The analyses are repeated for PE, PE10, and PE30 defined as above except including both cohorts pooled together in the analysis. Interaction tests are done to assess whether these PE parameters differ by cohort. All analyses that include both cohorts in the analysis allow a separate control group cumulative incidence of HIV-1 infection in the two cohorts (ie, cohort stratified analysis).

4.11.7 Assessment of individual-level markers of VRC01 mAb that correlate with protection against HIV infections (Secondary objective 1)

Secondary objective 1 is addressed based on the measurement of VRC01 mAb markers over time in mAb group breakthrough HIV-1–infected cases and in a random sample of HIV-1–uninfected mAb group participants (marker subset), integrated with the genotypic and phenotypic sieve analysis of breakthrough HIV-1 viruses accounting for knowledge of the VRC01 antibody footprint. The main analyses of the secondary objective 1 pool over the two mAb doses to maximize statistical power. Each of the objectives is assessed for each cohort separately and pooled across the two cohorts, and the analysis plan includes assessment of homogeneity of treatment effects across the two cohorts.

The design and results requirements for successful identification of correlates of protection in secondary objective 1 are:

1. Sufficient sample size to observe enough participants diagnosed with incident HIV-1 infection during the primary follow-up period of 80 weeks postenrollment in the mAb arms

2. A result of significant beneficial overall mAb PE > 0%
3. Sufficiently frequent HIV-1 testing schedule and accurate HIV-1 diagnostics
4. Wide variability in the concentration and effector functions of the mAb over time and/or individuals, and the ability to measure these characteristics such that their timing relative to the timing of HIV-1 acquisition is estimated with adequately low measurement error
5. mAb marker sampling design that allows sufficiently accurate PK modeling of mAb characteristics over time

Note that the serum concentration mAb markers (secondary endpoints 2) are defined without reference to a particular HIV-1 Env sequence. The effector function markers (also secondary endpoints 2) are relative to specific HIV-1 Envs or panels of Envs, and thus may be linked to immunogenicity endpoints that would be used in future trials of candidate HIV-1 vaccines. Correlates of protection analyses directly assess how mAb PE depends on markers.

4.11.7.1 Sampling of mAb markers

Characteristics of the mAb or immune responses to the mAb are measured in participants assigned to the mAb treatment groups. A ‘marker subset’ consisting of a random sample of 20% of the participants from each mAb group will be identified at entry based on a Bernoulli draw. Markers are measured from all HIV-1–infected cases in the mAb treatment groups and from HIV-1–uninfected participants in the marker subset for each of the mAb treatment groups who reach the Week 80 study visit HIV-1 negative. Based on the projected number of infections, the marker subset will result in approximately a 5:1 ratio of participants from the marker subset to cases for identifying correlates of protection. The timing of marker measurements is as follows:

- mAb group cases: The 2 timepoints closest to HIV-1 acquisition (last negative visit and first positive visit)
- mAb group marker subset: visits every 4 weeks through Week 80

4.11.7.2 Overview of the analysis of a mAb marker as a correlate of protection

For a given mAb recipient, let $S(t)$ be a marker characteristic at time t postenrollment in days, for example the time-concentration curve. The entire curve $S(t)$ cannot be known exactly given that the marker is measured at a grid of time-points. A PK model will be used to express $S(t)$ as a function of the measured marker readouts and error terms. The correlates of protection analysis will estimate the “prevention efficacy curve” $PE(S(t) = s)$ defined as

$$PE(S(t) = s) = [1 - (\text{hazard-mAb}(S(t) = s))/(\text{hazard-control}(S(t) = s))] \times 100\%$$

where $\text{hazard-mAb}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to either mAb group with $S(t) = s$ and $\text{hazard-control}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to the control group who would have had $S(t) = s$ had s/he been assigned to the same mAb group (thus $S(t)$ is a counterfactual random variable for control recipients). Similar parameters are used for assessing time-dependent correlates of protection in vaccine efficacy trials. A time-

dependent parameter is used because interest centers on understanding how the current value of a mAb marker associates with the level of instantaneous PE given exposure with an HIV-1 virus at that time. The statistical analysis plan will describe the methods used to estimate PE(s) over the range of values s of a mAb marker characteristic. In addition to estimation, hypothesis testing will be performed to assess whether a mAb marker modifies PE, ie, testing

$$H_0: PE(S(t) = s) = PE \text{ versus } H_1: PE(S(t) = s) \text{ varies in } s. \quad (1)$$

Rejecting H_0 in favor of H_1 supports the role of the marker in protection. The correlates of protection analysis pools over the two mAb groups, for the purpose of improving power both through a larger sample size and through greater inter-individual variability of the mAb markers.

4.11.7.3 A time-window approach to assessing mAb correlates of protection

For the two mAb groups pooled, HIV-1 incidence during the first 4 weeks of the infusion intervals (ie, weeks 1-4, 9-12, 17-20, ..., 73-76) is compared to HIV-1 incidence during the second 4 weeks of the infusion intervals (ie, weeks 5-8, 13-16, 21-24, ..., 77-80); these comparisons aggregate over all ten 8-week infusion intervals. The mAb concentration is known to be substantially higher during the first halves of the infusion intervals compared to during the second halves, therefore providing a test of whether and how much this difference correlates with a different level of PE.

4.11.7.4 mAb markers

For effector function markers measured based on a sample from a mAb recipient, the markers are measured to each of a panel of HIV-1 Envelope proteins. The most relevant HIV-1 Env panel represents the VRC01 antibody footprint diversity of viruses exposing trial participants. For example, relevant for the North/South American MSM + TG cohort, Figure 4-12 shows a logo plot of the VRC01 antibody footprint motifs comprising sixteen amino acid sites [18] based on 275 subtype B US and South American sequences deposited in the Los Alamos National Laboratory (LANL) sequence database between 2006 and 2014. There are 89 unique mAb footprints, 23% of which are unique, and the top 5 ranking footprints cover 53% of the 89 unique footprints.



Figure 4-12 Logo plot of the VRC01 antibody footprints that occur in 275 subtype B US and South American sequences deposited in the LANL sequence database between 2006 and 2014

During the conduct of the trial the research team will determine a minimal set of Envs constituting a panel capturing most of the VRC01 mAb footprint diversity of exposing viruses, for each cohort which may require separate panels for subtype B viruses and subtype C viruses. One effector function marker of interest for assessing as a correlate of

protection is the weighted area under the magnitude-breadth neutralization curve of the mAb footprint Env panel, where the weighting is by the estimated prevalence of mAb footprints in HIV-1s circulating at the trial sites during the trial.

For mAb group participants with a primary study endpoint (breakthrough HIV-1 infection during the first 80 weeks), an important marker is the level at which his/her pre-infection sample at the time of HIV-1 acquisition neutralizes his/her particular breakthrough virus. (This analysis requires modeling the marker at the time of HIV-1 acquisition based on the available grid of marker measurements.) A result where sera from infected participants generally fail to neutralize their founding viruses would support neutralization as a correlate of protection. This analysis is repeated for other effector functions as a way to discriminate which effector functions are or are not correlates of protection, and to rank the effector functions by their contribution to explaining the level of protection.

4.11.7.5 Power calculations for assessing a mAb marker as a correlate of protection

The marker $S(t)$ must vary over time and/or among mAb recipients in order to detect a correlate of protection, with more variability in one or both components providing greater statistical power to detect a correlate of protection via testing the null hypothesis of equation/panel (1) above. In essence, to detect correlates of protection it is necessary that a large fraction of person-years at risk are in high protection zones and a large fraction of person-years at risk are in low protection zones. (A “high protection zone” is a period of time during which a mAb recipient has high levels of a marker and high levels of efficacy.) Data from VRC 601 and VRC 602 show wide variability in the mAb concentration over time, and much more limited variability among mAb recipients. HVTN 104 will provide more data on these two aspects of marker variability. The limited among-mAb recipient variability motivates the study design that randomly assigns participants to 2 different mAb doses in order to create variability.

Achieving adequate power to detect correlates of protection requires that the HIV-1 diagnostic testing is more frequent than the infusion schedule. This is why diagnostic visits every 4 weeks are advantageous given infusions every 8 weeks, and procedures may be determined and applied to test for HIV-1 infection more frequently than every 4 weeks. The data from all of the diagnostic testing procedures will be incorporated into the modeling of $S(t)$ and into the statistical analysis for estimation and testing of $PE(S(t) = s)$. Lastly, achieving adequate power to detect correlates of protection requires studying markers that can be measured with a high ratio of potentially protection relevant variability versus protection irrelevant variability, where the latter variability could stem from technical measurement error of the assay or to error in estimation of the timing of infection. Because of this fact the trial design relies on parallel assay studies to qualify marker variables for the analysis and relies on development and characterization of models for $S(t)$ over continuous time t .

We provide one power calculation for assessing a trichotomous marker $S(t)$, the concentration of the mAb at time t post enrolment, as a correlate of protection, which divides the pooled mAb group at a given time t by two thresholds of marker response [$S(t) = 0$ indicates Low, $S(t) = 1$ indicates Medium, and $S(t) = 2$ indicates High for some pre-set definitions of Low, Medium, High]. Thus at any given time t after entry, $S(t)$ divides the pooled mAb group into three subgroups. In our illustration we take “0” to be a VRC01 serum concentration ≤ 50 mcg/mL, “2” to be a VRC01 serum concentration > 10 μ g/mL, and “1” to be an intermediate serum concentration.

Based on Figure 2-4, we conduct a power calculation indexed by the percentage of person-years at-risk of mAb recipients that are in the (Low, Medium, High) zones, and indexed by the level of PE within each of these zones. As indicated in the figure, we expect that about (50%, 40%, and 10%) of the PYRs at risk in the 10 mg/kg mAb group are in the (Low, Medium, and High) regions whereas about (10%, 40%, and 50%) of the PYRs at risk in the 30 mg/kg mAb group are in the (Low, Medium, and High) regions. We consider power calculations pooling data across both mAb groups and both cohorts, assuming 58 mAb HIV-1-infected cases with data and 290 mAb group HIV-1-uninfected controls with data, assuming the design alternatives $PE_{10} = PE_{30} = 60\%$ following the numbers displayed in Table 4-4. The detailed mathematical assumptions of these power calculations will be provided in the statistical analysis plan.

Figure 4-13 shows power curves for the scenario that (30%, 40%, 30%) of PYRs at risk are in the (Low, Medium, High) zones (which we approximately expect to occur based on Figure 2-4) and $PE_{10} = PE_{30} = (30\%, 60\%, 80\%)$ in these zones. The power curves also account for noise in the measurement of $S(t)$ via a parameter ρ that equals the proportion of the inter-individual marker variability that is potentially protection relevant. The results show that the noise level majorly affects power, underscoring that only assays meeting qualification criteria will be studied as correlates. The results also show that for a reasonably tight assay ($\rho = 0.7$), there is about 70% power to detect a correlate of protection (with effect size 30%, 60%, 80% efficacy) at the selected trial sample size. A more extensive set of power calculations will be conducted based on HVTN 104 study data.

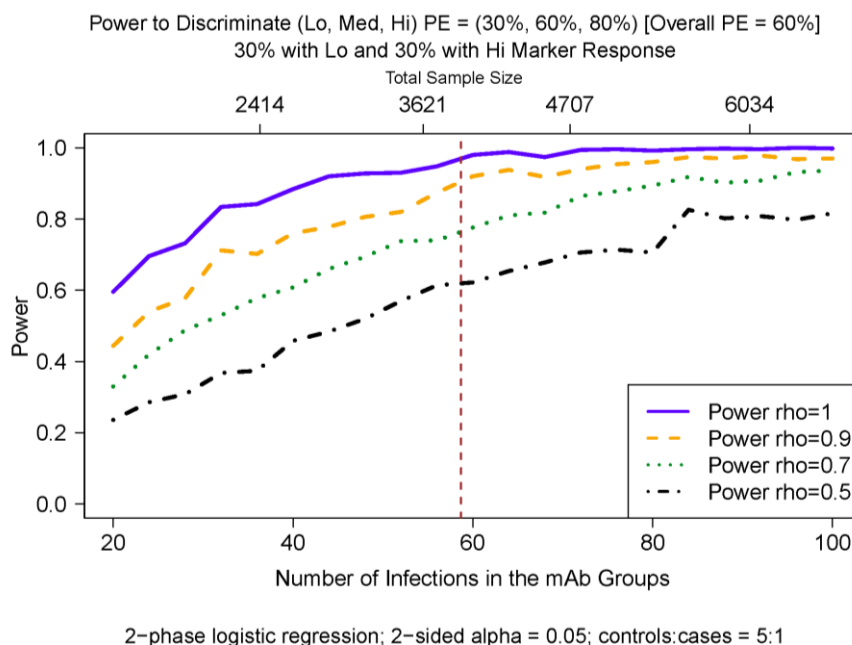


Figure 4-13 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)=\text{Low}$, $S(t)=\text{Medium}$, and $S(t)=\text{High}$, for a marker with assay noise parameter $\rho = 1$ (perfect marker), 0.9, 0.7, and 0.5 and percentages of person-years at risk in the (Low, Medium, High) marker regions set at (30%, 40%, 30%). The calculations assume 58 mAb group HIV-1-infected cases and 290 mAb group HIV-1-uninfected controls with data on $S(t)$ and pool over both mAb groups and over both cohorts. The dashed vertical line represents the sample size of the study.

Figure 4-14 shows the same power analysis as Figure 4-13, fixing $\rho = 0.9$ (indicating a qualifying assay) and varying the percentage of PYRs at risk that are in the (Low,

Medium, High) zones. The results show that power increases sharply with the percentage of mAb recipients that are in the Low and High regions, demonstrating the principle that variability in the marker is a strong determinant of power to detect a correlate of protection.

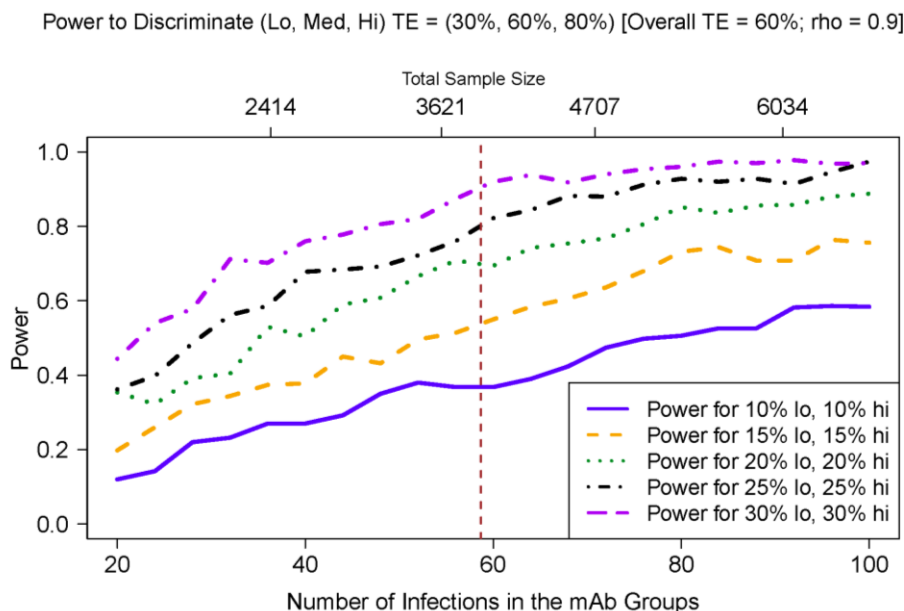


Figure 4-14 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups S(t) = Low, S(t) = Medium, and S(t) = High, for a marker with assay noise parameter rho = 0.9 and percentages of person-years at risk in the Low and High marker regions varied from 10%, 15%, 20%, 25%, 30%. The calculations assume 58 mAb group HIV-1-infected cases and 290 mAb group HIV-1-uninfected controls with data on S(t) and pool over both mAb groups and over both cohorts.

4.11.7.6 Genotypic and phenotypic sieve analysis

Genotypic sieve analysis analyzes sequences of breakthrough HIV-1 infecting viruses from the earliest available postinfection sample and seeks to identify amino acid “signatures” that differentiate mAb footprint breakthrough sequences in the mAb groups versus the control group, in terms of differential PE against HIV-1s according to some genotypic characteristics. For example, the genotypic sieve analysis assesses differential PE against different genotypes of HIV-1 with genotype defined by:

- Number of mismatches to the VRC01 mAb footprint
- Number of known mAb neutralization escape mutations in the mAb footprint
- Number of known mAb effector function escape mutations in the mAb footprint for non-neutralization effector functions such as ADCC, virion capture, and phagocytosis
- Number of potential N-linked glycosylation (PNG) sites within a given radius of the mAb footprint
- Length of variable loops in proximity to the mAb footprint

To illustrate the utility of genotypic sieve analysis, we consider a hypothetical result that would support that the mAb protects via specific neutralization targeting of the mAb's epitope. In this illustration, the HIV-1 genotype is defined by four ordered genotypes according to whether there are 0, 1, 2, or >2 neutralization escape mutations in the VRC01 mAb antibody footprint. The hypothetical result would be an estimated PE of 95% against HIV-1s with zero escape mutations and a PE of 0% against HIV-1s with >2 neutralization escape mutations, and intermediate and monotone decreasing level of estimated PE against HIV-1 with one mutation and two mutations, respectively.

A second type of sieve analysis, phenotypic sieve analysis, compares breakthrough viruses between the mAb versus control groups using an immunological assay. Specifically, data from an “effector function checkerboard” is filled out, with the rows representing serum samples from a random sample of mAb recipients HIV-1 uninfected at the time of sampling, and the columns representing HIV-1 Env VRC01 footprint targets created from the breakthrough viruses. The phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to mAb recipient sera between the mAb and control treatment groups. A second version of the phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to the VRC01 mAb between the treatment groups; this latter analysis is simpler, based on a single column of data instead of a matrix, because it does not use mAb recipient sera. For an example of the second type of phenotypic sieve analysis, the TZM-bl neutralization assay could be performed on all control breakthrough HIV-1s versus VRC01 and on all mAb group breakthrough HIV-1s (pooled over the two mAb groups and two cohorts) versus VRC01, and a Wilcoxon rank sum test applied to assess a difference. Reduced TZM-bl neutralization sensitivity of the mAb breakthrough group viruses would support that neutralization had a role in protection and that the TZM-bl assay was able to detect this role, and would support using the TZM-bl assay as a tool for evaluating future candidate HIV-1 vaccines. The HVTN has previously conducted neutralization sieve analysis [123]. Figure 4-15 illustrates a genotypic and phenotypic sieve analysis.

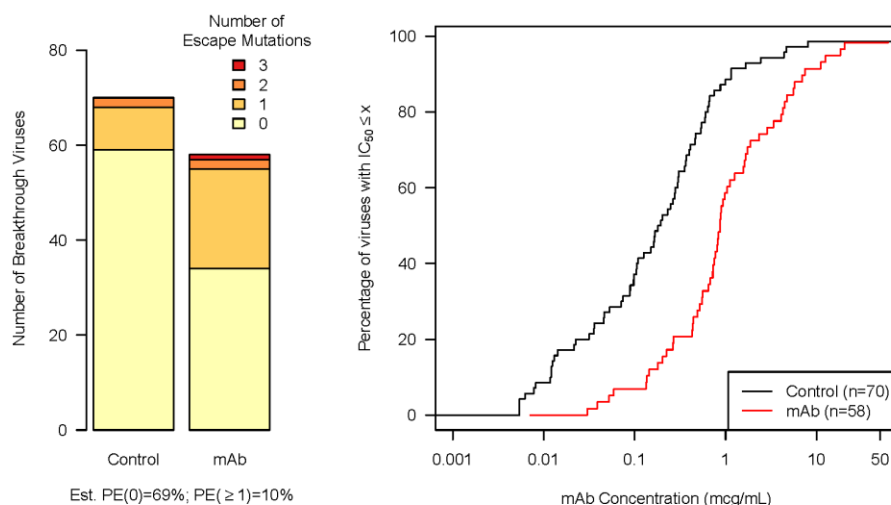
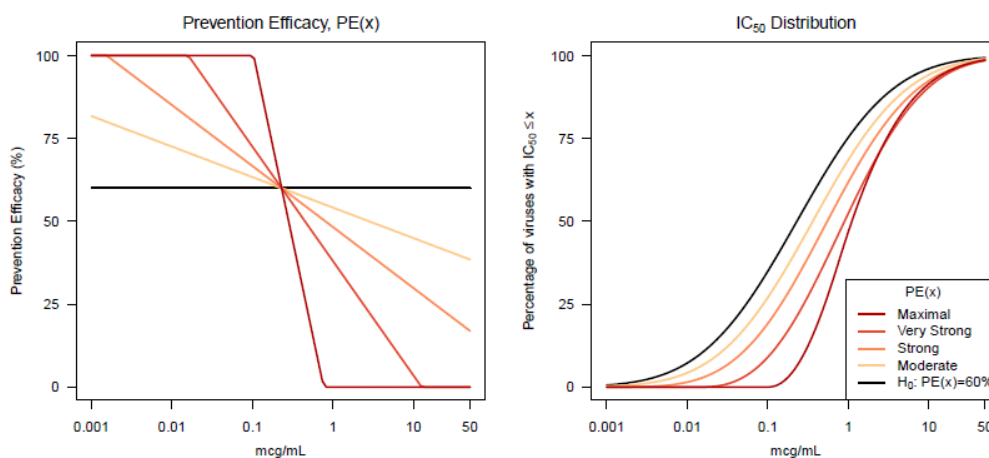


Figure 4-15 Illustration of genotypic (left panel) and phenotypic (right panel) sieve analysis, where the left panel shows the distribution of the number of known neutralization escape mutations in breakthrough control and mAb group HIV-1 sequences, and the right panel shows the percentage of the panel of breakthrough HIV-1s that are neutralized at level 50% (IC₅₀) by the given concentration of the VRC01 mAb.

4.11.7.7 Illustration of power to detect a phenotypic sieve effect

We conduct power calculations based on TZM-bl neutralization IC_{50} values (in mcg/mL) of VRC07 (a close cousin of VRC01) to approximately 100 viruses representing global HIV-1 diversity (data provided by Mark Louder, Robert Bailer, and John Mascola from the VRC). From the control group we sample 70 HIV-1 infections with IC_{50} from the VRC07 data set, and from the pooled mAb group we sample 58 HIV-1 infections with IC_{50} values bias sampled based on IC_{50} -dependent PE, with $PE(x)$ the probability an infected control recipient would be infected had they received the mAb with IC_{50} value of x to the exposing virus. Figure 4-16 shows power for comparing the VRC01 IC_{50} distribution of the pooled mAb group HIV-1s versus the control group HIV-1s, based on a two-sample Wilcoxon rank sum test. The effect size indexing a difference between the two groups is equivalently expressed in terms of the $PE(x)$ function (where a horizontal line indicates the null hypothesis of no difference) or in terms of a different cumulative distribution function of the IC_{50} in the two groups. The results show that, pooling over the cohorts, there is high power to detect ‘strong’ phenotypic sieve effects (third steepest curve in Figure 4-16), and within individual cohorts there is high power to detect ‘very strong’ phenotypic sieve effects (second steepest curve in Figure 4-16).



Power of Wilcoxon test (2-sided 0.05 level test)				
PE(x)	Number of control cases			
	50	60	70	80
Maximal	99.6	99.9	>99.9	>99.9
Very Strong	91.4	95.2	97.7	98.8
Strong	49.9	56.9	64.3	70.5
Moderate	16.6	18.5	21.4	24.2
H ₀ : PE(x)=60%	5.2	5.2	5.1	4.9

Figure 4-16 Power calculations for comparing IC_{50} distributions between mAb group breakthrough HIV-1s and control group breakthrough HIV-1s, with difference equivalently expressed in terms of the $PE(x)$ curve or the cumulative IC_{50} distribution functions, where in the right panel the black/highest curve represents the distribution for the control group breakthrough HIV-1s.

5 Selection and withdrawal of participants

Participants will be healthy, HIV-uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or serum mAb concentration and efficacy difficult, and some volunteers may be poor candidates for retention.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections 5.1 and 5.2.

5.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 50 years
2. **Access to a participating CRS** and willingness to be followed for the planned duration of the study
3. Ability and willingness to provide **informed consent**
4. **Assessment of understanding:** volunteer demonstrates understanding of this study and completes a questionnaire prior to first infusion with verbal demonstration of understanding of all questionnaire items answered incorrectly
5. **Agrees not to enroll in another study** of an investigational research agent for the duration of the participant's trial participation
6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

7. Willingness to receive **HIV test results**
8. Willingness to **discuss HIV infection risks** and amenable to HIV risk reduction counseling

9. **In the Americas, persons born Male or identifying as Transgender (TG)** who, in the 6 months prior to randomization, experienced 1 or both of the following HIV risk criteria:

- Condomless anal intercourse with 1 or more male or transgender partner(s)
- Anal intercourse with 2 or more male or transgender partners

Male-to-female and female-to-male TG volunteers are eligible. Receipt of hormonal therapy does not make a TG volunteer ineligible.

In Africa, persons born Female (assigned female sex at birth) and identifying as a female, who, in the 6 months prior to randomization, has had vaginal and/or anal intercourse with a male partner

In the Americas and Africa, all volunteers who have been in a monogamous relationship with an HIV-1 seronegative partner for > 1 year are excluded.

Laboratory Inclusion Values

Hematology

10. **Hemoglobin** (Hgb) ≥ 10.5 g/dL for volunteers who were born female, ≥ 13.0 g/dL for volunteers who were born male
11. **Platelets** $\geq 100,000$ cells/mm³

Chemistry

12. **ALT** < 2.5 times the institutional upper limit of normal and creatinine ≤ 1.25 times the institutional upper limit of normal

Virology

13. **HIV uninfected, as defined in the SSP, within 30 days prior to enrollment**

Urine

14. **Negative, trace, or 1+ urine protein by dipstick**

Reproductive Status

15. **Volunteers capable of becoming pregnant:** negative serum or urine beta human chorionic gonadotropin (β -HCG) pregnancy test performed at the screening visit and prior to infusion on the day of initial infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.
16. **Reproductive status:** A volunteer who is capable of becoming pregnant must agree to consistently use effective contraception (see Appendix B, Appendix C, and SSP) for

sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit.

17. **Volunteers capable of becoming pregnant must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

5.2 Exclusion criteria

General

1. **Investigational research agents** received within 30 days before first infusion
2. **Body mass index (BMI) ≥ 40**
3. **Pregnant or breastfeeding**
4. **Any reactive, indeterminate, or positive HIV test**, even if subsequent testing indicates that the individual is not HIV infected.

Monoclonal antibodies and vaccines

5. **Previous receipt of humanized or human mAbs**, whether licensed or investigational
6. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 703/HPTN 081 PSRT will determine eligibility on a case-by-case basis.

Immune System

7. **Serious adverse reactions to VRC01 formulation components such as sodium citrate, sodium chloride, and L-arginine hydrochloride**, including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.
8. **Autoimmune disease**, including Type I diabetes mellitus (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require consistent immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate reactogenicity and AE assessments)
9. **Immunodeficiency syndrome**

Clinically significant medical conditions

10. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:

- Any contraindication to repeated infusions or blood draws, including inability to establish venous access;
 - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period; or
 - A condition or process for which signs or symptoms could be confused with reactions to VRC01.
11. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence, assessment of safety or infusion reactions, or a volunteer's ability to give informed consent
 12. **Psychiatric condition that precludes compliance with the protocol.** Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
 13. **Asthma**, other than mild, well-controlled asthma
 14. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
 15. **Malignancy** (Not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure. or who is unlikely to experience recurrence of malignancy during the period of the study)
 16. **Seizure disorder:** History of seizure(s) within past three years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.
 17. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema
 18. History of **organ or tissue transplantation**
 19. **Known hepatic or renal dysfunction**

5.3 Participant departure from infusion schedule or withdrawal

This section concerns an individual participant's departure from the infusion schedule. Pause rules for the trial as a whole are described in Section 10.2.4.

5.3.1 Delaying infusions for a participant

Under certain circumstances, a participant's scheduled infusion will be delayed. The factors to be considered in such a decision include but are not limited to the following:

- Prior to infusion, abnormal vital signs or clinical symptoms that may mask assessment of a study product reaction

- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delay or withdrawal from the infusion schedule. The investigator may consult with the HVTN 703/HPTN 081 PSRT.
- Pregnancy: for participants who become pregnant infusions will be stopped. If the participant is no longer pregnant (as demonstrated by a negative urine or serum pregnancy test) and wants to continue with infusions, the HVTN 703/HPTN 081 PSRT will be consulted to determine whether the participant may resume infusions or whether infusions should be permanently discontinued.

5.3.2 Participant departure from infusion schedule

Every effort should be made to follow the infusion schedule per the protocol. If a participant misses an infusion and the visit window period for the infusion has passed, then sites may consult the SSP.

5.3.3 Discontinuing infusions for a participant

Under certain circumstances, an individual participant's infusions will be permanently discontinued. Specific events that will result in stopping a participant's infusion schedule include:

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of infusions may be granted with the unanimous consent of the HVTN 703/HPTN 081 PSRT).
- Clinically significant condition (ie, a condition that affects the immune system or for which continued infusions and/or blood draws may pose additional risk), including but not limited to the following:
 - Any grade 4 local or systemic reactogenicity symptom or AE that is subsequently considered to be related to study product;
 - An SAE that is subsequently considered to be related to study product;
 - Any grade 3 clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to study product;
 - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product;
 - Clinically significant hypersensitivity reaction including but not limited to type 1 hypersensitivity reaction and/or serum sickness associated with study product. Consultation with the HVTN 703/HPTN 081 PSRT is required prior to subsequent infusion following any hypersensitivity reaction associated with study product; or
- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).

Such participants should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated.

In addition, infusions will be permanently discontinued for a participant diagnosed with HIV infection or with 2 reactive HIV tests, even if subsequent testing indicates that the participant is not HIV infected (see Appendix G and Appendix J).

5.3.4 Participant termination from the study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation
- Participant relocates and remote follow-up or transfer to another CRS is not possible
- CRS determines that the participant is lost to follow-up
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff)
- Any condition where termination from the study is required by applicable regulations.

6 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 1-1. See the IBs for further information about study products.

6.1 Study product regimen

The schedule of study product administrations is shown in Section 1 and additional information is given below.

Cohort: North + South American MSM and TG

Group 1

Treatment 1 (T1): VRC-HIVMAB060-00-AB 10 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 2

Treatment 2 (T2): VRC-HIVMAB060-00-AB 30 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 3

Control 3 (C3): Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) to be administered as a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Cohort: Sub-Saharan African Women

Group 4

Treatment 4 (T4): VRC-HIVMAB060-00-AB 10 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 5

Treatment 5 (T5): VRC-HIVMAB060-00-AB 30 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to administer a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 6

Control 6 (C6): Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) to be administered as a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

6.2 Study product formulation

VRC-HIVMAB060-00-AB [VRC01, Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB]

VRC01 will be provided as a sterile clear, colorless to yellow isotonic solution with no visible particles. Each vial contains 100 mg / mL of VRC-HIVMAB060-00-AB in formulation buffer. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and do NOT contain a preservative. The product should be stored frozen (-45°C to -10°C). The study products are described in further detail in the IB.

VRC01 is a highly concentrated protein solution and may develop white-to-translucent particles after thawing. These particles have been observed in approximately 1-3% of the vials and generally disappear over a few hours at room temperature. This particle formation has no effect on product quality.

Control for VRC01 [Sodium Chloride for Injection USP, 0.9%]

Sodium Chloride for Injection USP, 0.9% will be used as the Control for VRC01. It must be stored as directed by the manufacturer. For sites who do not have access to Sodium Chloride for Injection USP, 0.9%, the Sodium Chloride for Injection, 0.9% that they use must meet the following criteria: a sterile solution of Sodium Chloride in Water for Injection which contains no antimicrobial agents. It is nonpyrogenic and is intended for intravenous administration.

6.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription MUST contain the participant's weight based upon the participant's weight at the most recent visit where weight was measured (this includes screening) and randomization code (this may NOT be communicated verbally). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 38 General Chapter Physical Tests / <797> Pharmaceutical

Compounding - Sterile, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

6.3.1 VRC-HIVMAB060-00-AB (10mg/kg IV) - (Groups 1 and 4)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($10 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. The pharmacist, using aseptic technique, will add the appropriate amount of VRC01 to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will add the appropriate volume of Sodium Chloride for Injection USP, 0.9% to the same bag which now contains VRC01 in Sodium Chloride for Injection USP, 0.9% for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.2 VRC-HIVMAB060-00-AB (30mg/kg IV) - (Groups 2 and 5)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($30 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. The pharmacist, using aseptic technique, will add the appropriate amount of VRC01 to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will add the appropriate volume of Sodium Chloride for Injection USP, 0.9% to the same bag which now contains VRC01 in Sodium Chloride for Injection USP, 0.9% for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.3 Control for VRC01 (Groups 3 and 6)

To prepare an IV infusion, the pharmacist, using aseptic technique, will add 50 mL of Sodium Chloride for Injection USP, 0.9% to a 100 mL bag of Sodium Chloride for

Injection USP, 0.9%. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”.

6.4 Administration

VRC01 or Control (Intravenously)

The investigational study product solution will typically be administered IV over about 30 to 60 minutes using a volumetric pump of 150 mL. The total time needed to administer the dose may be longer based on factors such as participant tolerance.

6.5 Acquisition of study products

VRC-HIVMAB060-00-AB is provided by the VRC/DAIDS/NIAID.

Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) will not be provided through the protocol and must be obtained by the site.

Once a CRS is protocol registered, the pharmacist can obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) by following the ordering procedures given in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

6.6 Pharmacy records

The CRS pharmacist is required to maintain complete records of all study products. The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

6.7 Final disposition of study products

All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the CRPMC. The procedures and relevant form are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

7 Clinical procedures

The schedules of clinical procedures are shown in Appendix I through Appendix K.

7.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The informed consent form documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in this study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the participant and the review should be documented. At each study visit, CRS staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information is learned that might affect the participants' decisions to stay in the trial, this information will be shared with trial participants. If necessary, participants will be asked to sign revised informed consent forms.

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to IRB/EC and any applicable RE for human subjects protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is “Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs [informed consent forms] prior to implementation at a site.” CRSs are responsible for knowing the requirements of their applicable REs.

7.1.1 Screening consent form

Without a general screening consent, screening for a specific study cannot take place until the site receives protocol registration from the DAIDS RSC Protocol Registration Office.

Some CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV prevention trial. In this way, CRS staff can continually screen potential participants and, when needed, proceed quickly to obtain protocol-specific enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time period specified in the eligibility criteria.

7.1.2 Protocol-specific consent forms

The protocol-specific consent forms describe the study products to be used and all aspects of protocol participation, including screening and enrollment procedures. A sample protocol-specific consent form for the main study is located in Appendix A. A separate sample consent form for other uses of specimens is located in Appendix D.

Each CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in Appendix A and Appendix D. The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC, and any applicable RE
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their site-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the level of understandability.

The sample informed consent form includes instructions throughout the document for developing specific content.

Sites should follow the instructions in the Protocol-specific Official Memo distributed along with this protocol regarding when they may begin using their site-specific protocol consent forms.

Regarding protocol registration, sites should follow procedures outlined in the current version of the DAIDS Protocol Registration Manual.

7.1.3 Assessment of Understanding

Study staff are responsible for ensuring that participants fully understand the study before enrolling them. This process involves reviewing the informed consent form with the participant, allowing time for the participant to reflect on the procedures and issues presented, and answering all questions completely.

An Assessment of Understanding is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary. Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

IRB/EC and any applicable RE may require that a participant has signed either a screening or protocol-specific consent document prior to administering the Assessment of Understanding. The consent process (including the use of the Assessment of

Understanding) should be explained thoroughly to the IRB/EC and any applicable RE, whose recommendations should be followed.

7.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before infusion on Day 0. All inclusion and exclusion criteria must be assessed within 56 days before enrollment, with the exception of HIV testing, which must be performed within 30 days before enrollment (see Section 5.1), unless otherwise specified in the eligibility criteria (or below in this section).

After the appropriate informed consent has been obtained and before enrollment, the following procedures are performed:

- Medical history, documented in the case history record;
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots (record the complete generic name for all medications);
- Laboratory tests as defined in the inclusion and exclusion criteria, including:
 - Screening HIV testing at local lab (see SSP)
 - CBC with differential
 - ALT
 - Creatinine
 - Urine dipstick
 - Urine or serum pregnancy test (volunteers capable of becoming pregnant); Persons who are not capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Assessment of participant risk for HIV infection
- Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>);
- Counseling on HIV testing and risk reduction, performed in compliance with US CDC current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 7.5; and

- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in the study inclusion criteria and in the SSP. Discussion of pregnancy prevention includes advising a participant who was born female and who reports no current sexual activity that could lead to that participant becoming pregnant to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

7.2.1 Use of screening results from another HVTN or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this study, and the tests were conducted within the time periods specified in the eligibility criteria (see Section 5).

7.3 Enrollment and infusion visits

Enrollment is simultaneous with first infusion. The time interval between randomization and enrollment should not exceed 4 working days. The CRS requests the randomization assignment from the Web-based randomization system. Circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all infusion visits, the following procedures are performed before infusion:

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Assessment of baseline reactogenicity parameters;
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- Assessment of concomitant medications (as described in Section 7.2);
- ALT
- Creatinine
- CBC with differential
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having

undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and

- Blood collection for HIV testing and sample storage.

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (see Sections 6.3 and 6.4).

Administration of an infusion and infusion-related procedures must be accomplished within 1 calendar day.

Immediately following the first infusion, the participant remains in the clinic for observation. An initial reactogenicity assessment is made after completion of the first infusion and as needed for subsequent infusions. For further detail regarding the infusion visit protocol that CRSs must follow, see the SSP.

Before leaving the clinic, the participant is given the postinfusion symptom log and is instructed on how to complete it. The site will make arrangements to obtain a report of reactogenicity events from the participant after the 3-day reactogenicity period (as described in Section 7.8 and in the SSP).

The following procedures will be performed at all infusion visits. These procedures may be performed prior to, during, or following infusion:

- Administration of the participant questionnaire which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling);
- Risk reduction counseling (as described in Section 7.5);
- Pregnancy prevention assessment (as described in Section 7.2 and 7.6);
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled visits as specified in Appendix I:

- Rapid plasma reagin (RPR),
- Urine gonorrhea (GC)/chlamydia,
- Rectal GC/chlamydia (North + South American MSM & TG only),
- Trichomonas (sub-Saharan African women only), and

- Urine dipstick.

7.4 Follow-up visits

The following procedures are performed at all scheduled follow-up visits:

- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Blood collection for HIV testing and sample storage.
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled follow-up visits as specified in Appendix I through Appendix K:

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Administration of participant questionnaire, which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling)
- Risk reduction counseling (as described in Section 7.5);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Pregnancy prevention assessment (as described in Section 7.2 and 7.6);
- Assessment of new or unresolved AEs/intercurrent illnesses; and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.5 HIV counseling and testing

HIV counseling will be performed in compliance with the CDC's guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the protocol-specific HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection. In addition, study participants will be provided with HIV prevention supplies and referral to providers of PrEP per local and regional guidelines. Study investigators will ensure that participants have access to standards of care for HIV prevention in their local settings. As new data emerge and standards of care for HIV prevention evolve, both the content of risk reduction counseling and referrals for biomedical interventions will be updated to conform to current best practices for each of the cohorts enrolled in this trial. For additional details regarding PrEP provision and referrals, see the SSP.

7.5.1 Study product–related seroreactivity

Human sera containing purified VRC01 at concentrations up to 200 mcg/mL have been tested using a variety of commercially available HIV test kits without any indication of reactivity. For this reason, we do not anticipate that receipt of VRC01 will cause a reactive result on currently available HIV test kits, but this remains a theoretical possibility.

Because this possibility cannot be categorically eliminated, study staff will advise study participants to confine their HIV testing while in the study to that provided through the CRS. Staff will also inform study participants of the likelihood of routine HIV testing being offered or performed outside the study CRS at emergency rooms, clinics, and medical offices and will inform participants of their right to opt out of HIV testing outside the study site. CRS staff should inform study participants if local and/or state/regional policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline testing preemptively. CRS staff should also inform participants if positive results must be reported to local public health authorities. CRS staff should also inform participants of the need to maintain study blinding by getting HIV testing only at the study CRS. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV mAb clinical trial and should only be tested at the study CRS.

Study staff should also stress that the study product is completely cleared from the body within a few months, so even the theoretical risk of VRC01 causing a misleading HIV test result will disappear before their final scheduled clinic visit.

7.6 Contraception status

Contraception status is assessed and documented at screening and infusion visits for a participant who is capable of becoming pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. These participants should be reminded regularly of the importance of using contraception and should be referred to specific counseling, information, and advice as needed. (Specific contraception requirements are listed in the SSP). This reminder should be documented in the participant's study record.

Infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation—must be documented in the participant's study record.

7.7 Urine testing

Dipstick testing may be performed in the clinic or the lab, as long as the required elements are tested. The examination is performed on urine obtained by clean catch.

If the dipstick is transiently abnormal due to menses or infection, document this issue in the participant's source documentation. For infection, provide appropriate treatment and/or referral. If the dipstick was performed for screening then repeat the dipstick following resolution and, if within the eligibility limits specified in the protocol, the participant may be enrolled.

A follow-up urine test should be deferred if a participant is menstruating, but should be performed as soon as possible. If a follow-up dipstick is abnormal due to a participant's menstrual period, document in the comment section of the CRF and repeat the dipstick once the participant is no longer menstruating. A micro-urinalysis is not required.

7.8 Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after infusions per the SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0, November 2014, except as noted in Section 10.2.2.

The reactogenicity assessment period is 3 full days following infusions. Participants are instructed to record symptoms using a postinfusion symptom log. The site staff and the participant will be in contact after the 3-day reactogenicity period, or sooner if indicated, to review reactogenicity data. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. Participants are instructed to contact the clinic for events that arise during the period between infusion and the next scheduled visit. In general, a participant who self-reports any postinfusion reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity events are reported using CRFs that correspond to the time of assessment per the SSP. Reactogenicity assessments include assessments of systemic and local symptoms and infusion-related lesions. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of infusion and 3 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse experience log form.

7.8.1 Assessment of systemic and local symptoms

Systemic symptoms include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, pruritus, diarrhea, and vomiting. Local symptoms include pain and/or tenderness proximal to the infusion site. The daily maximum severity reached for each symptom during the assessment period is reported.

7.8.2 Assessment of infusion site

Infusion site reactions may include redness/erythema induration/swelling, and phlebitis. The maximum horizontal and maximum vertical measurements for all infusion site reactions are recorded.

All infusion site reactions are monitored until resolution. Areas greater than 25 cm² are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

7.9 Visit windows and missed visits

Visit windows are defined in the SSP. For a visit not performed within the window period, a Missed Visit form is completed. If the missed visit is one that required safety assessments or local safety labs, CRS staff should attempt to bring the participant in for an interim visit as soon as possible.

Procedures performed at an interim visit are usually toxicity/safety assessments (including local safety labs) and HIV testing. With the exception of HIV testing, these procedures are performed only if they were required at the missed visit or if clinically indicated. HIV testing may be performed as deemed appropriate by the study staff.

If a participant missed an infusion visit or if infusions must be permanently discontinued, see Section 5.3.2 and Section 5.3.3 for resolution.

7.10 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, ALT, and Creatinine), pregnancy testing, social impact assessment, and HIV test.

7.11 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given during the pregnancy, but remaining visits and study procedures should be completed unless medically contraindicated. For participants who are no longer pregnant, see Section 5.3.1. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome.

8 HIV infection assessment and clinical response

8.1 HIV symptom assessment

At all scheduled visits and at unscheduled visits due to illness or suspected exposure, if necessary, information will be collected about any signs or symptoms suggestive of acute HIV infection. Participants will be counseled about signs and symptoms of acute HIV infection and at visits following recent high-risk exposure, participants will be queried about any signs/symptoms suggestive of acute HIV infection. Presence of signs/symptoms suggestive of acute HIV infection, an intercurrent illness consistent with acute retroviral syndrome, or history of high-risk exposure would prompt a diagnostic work-up per the protocol-specific algorithm for recent exposure to determine HIV infection.

8.2 HIV screening test (prior to randomization)

Prior to randomization, participants will be screened for HIV-1/2 infection by FDA-approved blood tests (non-US sites may use locally available assays that have been approved by HVTN and HPTN Laboratory Operations [see SSP]). Volunteers identified as being HIV infected during screening will be referred for medical treatment and management of the HIV infection. These individuals may also be referred to appropriate ongoing clinical trials or observational studies. For volunteers who have one or more reactive/positive HIV tests, but whose HIV status is inconclusive, any further testing will be performed locally.

8.3 HIV testing postinfusion

Following enrollment, HIV testing will take place at scheduled clinic visits (Appendix F).

HIV testing will be performed using the protocol-specific HIV testing algorithms (see SSP). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV 1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV 1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit (ie, visit #.X specified in Appendix G and Appendix H). Samples to be stored for future studies will also be collected at this time (see Appendix G).

A 'case' will be defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s) (Section 8.4).

The HVTN Laboratory Program is responsible for all in-study diagnostic testing.

8.4 Endpoint adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess. Therefore, this study will have an endpoint adjudication process to review all serological and virological test results in a blinded manner for each participant who tests positive per the HVTN 703/HPTN 081 HIV diagnostic testing algorithms. Adjudicators will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (ie, HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the VRC and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

8.5 HIV infection during the study

It is critical to the success of the study that HIV-infected participants be properly identified and all data postdiagnosis be carefully recorded. Information obtained from these cases of HIV-1 infection will form the basis of the primary endpoint assessment.

Participants who develop HIV infection following the initial infusion of study product may remain in the study for follow-up but will receive no further infusions. All participants who become HIV infected following enrollment through their final study visit will be monitored as indicated in Appendix G and Appendix J.

If a participant is confirmed to have become HIV infected after enrollment, plasma HIV-1 RNA will be measured on archived samples prior to the first positive screening test. HIV-1 RNA testing will also be performed at 1-week intervals up to 3 weeks postdiagnosis, then at 2-week intervals up to 7 weeks postdiagnosis, then at 4-week intervals up to 15 weeks postdiagnosis, then at 23 weeks postdiagnosis. In addition to plasma HIV-1 RNA testing, participants will also have specimens drawn for measurements of VRC01 Ab serum levels, neutralization and other antibody functions, viral isolation and sequencing; physical exams, recording of AEs, counseling to reduce HIV transmission risk, and social impact assessments will also be performed at most of these visits.

Longer-term follow-up for these participants may be accomplished through enrollment in another protocol. Archived samples from earlier visits may also be tested to determine the earliest date of HIV infection.

If enrollment visit HIV testing indicates that a participant was HIV infected at enrollment (ie, prior to the first infusion of study product), then the procedures indicated in the preceding paragraph do not apply. Such participants should be followed as indicated in Appendix H and Appendix K.

8.6 Medical care for participants who become HIV infected

It is anticipated that some study participants, whether they are randomized to receive VRC01 or control, will become HIV infected during the course of the trial. It is critical that these HIV-infected participants receive appropriate medical care.

The investigators associated with this trial will refer participants who develop HIV infection while participating in this trial to medical professionals for care.

9 Laboratory

9.1 CRS laboratory procedures

The SSP provides further guidelines for operational issues concerning the clinical and processing laboratories. The manual includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix F through Appendix H. For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, laboratory special instructions will be posted on the protocol-specific section of the HVTN website.

9.2 Total blood volume

Required blood volumes per visit are shown in Appendix F through Appendix H. Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

9.3 Assay timepoints

Endpoint assays are performed on participants at the timepoints shown in Appendix F through Appendix H and may be performed at baseline. Assays for humoral and cellular responses may be performed on participants or a subset of participants at other timepoints; the schedules are shown in Appendix F through Appendix H.

9.4 VRC01 mAb levels

VRC01 levels will be measured in serum. An ELISA will be used to determine the concentration of the VRC01 antibody in the serum. The ELISA employs the VRC01 Fab-specific 5C9 mAb, which is an anti-idiotypic antibody cloned from a single B cell that was sorted by flow cytometry using a VRC01 scFv probe. The 4-parameter logistic curve regression of a standard curve of VRC01 covering the range from 0.031 to 1.0 mcg/mL is utilized in this assay to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay. This assay has been qualified but not formally validated. The functional sensitivity for the generation of the ELISA assay format, which is currently used at NVITAL, is 2 mcg/mL and as the technology for this assay continues to develop, an updated assay may be utilized.

9.5 Endpoint assays: humoral

9.5.1 Anti-VRC01 antibody assay

Assessment for development of anti-VRC01 antibodies in participants will be performed using the Forte Bio Octet BioLayer Interferometry (BLI) technology. The assay uses VRC01 immobilized to a biosensor. The biosensor is dipped into patient serum samples and antibodies against VRC01 are directly measured. The binding response is directly proportional to the anti-drug concentration as determined against a calibration curve using the 5C9 antibody.

9.5.2 Neutralizing antibody assay

Depending upon the concentrations measured in collected specimens, further evaluation of the research samples to assess for functional capacity to neutralize HIV in blood and mucosal secretions may be evaluated by an in vitro cell-based virus neutralization assay [124-126] using pseudotyped viruses.

One or more viruses that are among the most sensitive to VRC01 (eg, MN.3 and MW965.26) will be assayed. The IC_{50} of VRC01 against both of these viruses is 0.01 – 0.03 mcg/ml and the TZM-bl assay is validated for this level of sensitivity.

9.6 ARV detection

A direct, biomedical measure will be used to assess ARV use in this study. This approach will be used, since self-report of ARV use for PrEP or PEP and other purposes has been shown to be unreliable in a variety of settings [85,116,117]. For this study, ARV testing will be performed using a low cost, high-throughput, qualitative multi-drug assay developed at the HPTN Laboratory Center. This approach will allow detection of drugs that are FDA-approved for PrEP (FTC/TDF) as well as numerous other ARVs that may be used off-study/off-label for a variety of reasons (eg, PrEP, PEP, recreational use, hepatitis treatment). Testing will be performed retrospectively on batched samples. Individual test results will not be returned to study sites or study participants.

The methods that will be used for ARV testing are summarized here. Stored serum or plasma samples collected in the study will be tested for the presence of approximately 20 ARVs using an assay based on high resolution mass spectrometric (HRMS) analysis. The following ARVs were included in the assay when this document was prepared: 9 protease inhibitors (amprenavir, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir), 6 NRTIs (abacavir, emtricitabine, lamivudine, stavudine, tenofovir, zidovudine), 3 NNRTIs (efavirenz, nevirapine, rilpivirine), an integrase inhibitor (raltegravir), and an entry inhibitor (maraviroc). Each drug is identified and reported separately. The current limit of identification for each of the ARVs listed above is 10 ng/mL. The specific methods used for ARV detection may be modified (eg, to improve throughput) before samples from this study are tested.

9.7 Host (human) genotyping

Various markers, such as genes associated with host immune functions or HIV disease progression may also be assessed.

9.8 Lab assay algorithm

The HVTN Lab Assay Algorithm lists assays that characterize various types of immunologic activity as well as host genetics that may be conducted to characterize the drug activity in this study. Various types of assays may be employed to assess maintenance of functional drug activity at multiple timepoints selected based on drug level outcomes. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

9.9 Possible additional studies

Samples may be used for other testing and research related to furthering the understanding of HIV immunology, monoclonal antibodies, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

9.10 Other use of stored specimens

The Networks store specimens from all study participants indefinitely, unless a participant requests that specimens be destroyed or if required by IRB/EC or RE.

Other use of specimens is defined as studies not described in the protocol.

This research may relate to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases. This could include limited genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other testing on specimens will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs if required.

The protocol sample informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study site investigator or designee must notify HVTN Regulatory Affairs in writing. In either case, HVTN Regulatory Affairs directs the HVTN Lab Program not to use samples from these participants for such other uses.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on other use of specimens.

9.11 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

10 Safety monitoring and safety review

10.1 Safety monitoring and oversight

10.1.1 HVTN 703/HPTN 081 PSRT

The HVTN 703/HPTN 081 PSRT is composed of the following members:

- DAIDS medical officer representatives,
- Protocol chairs and cochairs,
- Protocol Team leader,
- Core medical monitor,
- Clinical safety specialist (CSS), and
- Regional medical liaison (RML).

The clinician members of HVTN 703/HPTN 081 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinators, project managers, study product developer representatives, clinical research manager, clinical trial manager, and others may also be included in HVTN 703/HPTN 081 PSRT meetings.

10.1.2 NIAID DSMB

The NIAID DSMB assesses the effects of the study product during the trial, provides other monitoring as described in Section 4.7.1.1, and may give advice to the HVTN 703/HPTN 081 Oversight Committee.

10.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 703/HPTN 081 PSRT and NIAID DSMB.

The roles and responsibilities of the HVTN CSS or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 703/HPTN 081 PSRT AE review criteria (see Section 10.2.4);

- Notifying CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 10.2.4);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 703/HPTN 081 PSRT.

10.2 Safety reporting

10.2.1 Submission of safety forms to SDMC

Sites must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, concomitant medications) before the end of the next business day after receiving the information. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information.

10.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation subject administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). The AE reporting period for this study comprises the entire study period for each individual participant (from study enrollment until study completion or discontinuation of the study). All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0. [November 2014], available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>, except that the AEs below will be reported according to the SSP:

- Weight loss
- Infusion Site Erythema or Redness and Infusion Site Induration or Swelling
- Insomnia

As detailed in the SSP, two additional parameters, cytokine release syndrome and serum sickness, have been added to the DAIDS AE Grading Table for HVTN 703/HPTN 081.

AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (Section 10.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 10.2.4).

Sites are expected to notify the CSS or RML of any serious safety concern requiring their attention (see Table 10-1). Telephone numbers and email addresses are found on the

HVTN703/HPTN 081 protocol-specific website. Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, the CSS or RML will reply during working hours (US Pacific Time) to confirm that the email has been received and reviewed. If email service is not available, the CRS should notify the CSS or RML of the event by telephone, then submit CRFs.

In addition, site investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

10.2.3 Expedited reporting of adverse events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE Manual), which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Event Reporting System (DAERS) must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

Sites where DAERS has not been implemented will submit expedited AE reports by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about expedited AE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

Under ICH E2A (*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*), an SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe),
- requires patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is a medically important event or reaction.

Medical and scientific judgment should be exercised when deciding if other situations are serious. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions not resulting in hospitalization, or development of drug dependency or drug abuse.

The expedited reporting period for this study comprises the entire study period for each individual participant (from study enrolment until study completion or discontinuation from the study).

The study products for which expedited reporting are required are:

- VRC01, and
- Control.

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

If the PSRT believes unblinding of the site PI to treatment assignment will assist with the clinical management of the SAE, the PSRT may consult the independent NIAID DSMB for a recommendation. In the event the PSRT and/or the NIAID DSMB determines that unblinding is indicated, the unblinded statistician, DSMB Chair, or designee will inform the site physician of the participant's treatment assignment in such a manner as to maintain the study blind of the PSRT and study team. For additional impact and management of SAEs on the study, refer to Section 10.2.4.

10.2.4 Expedited reporting of AEs to pertinent national regulatory authorities

The study sponsor or designee(s) prepares and files expedited reports to appropriate regulatory authorities within the timelines required by pertinent national regulatory authorities.

Site IoRs/designees will submit AE information and any other relevant safety information to their ECs/IRBs in accordance with EC/IRB requirements.

10.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and infusion with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 703/HPTN 081 PSRT AE review are summarized in Table 10-1. Infusions may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the HVTN 703/HPTN 081 PSRT, participant safety may be threatened. Criteria for an

individual participant's departure from the schedule of infusions are listed in Section 5.3.2.

Table 10-1 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	CRS action ^a	HVTN Core ^b action
SAE, related	Grade 4 or 5	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 703/HPTN 081 PSRT notification
SAE, related	Grade 3	E-mail and submit forms immediately	Prompt HVTN 703/HPTN 081 PSRT AE review to consider pause
AE ^c , related	Grade 4 or 3	Email and submit forms immediately	Prompt HVTN 703/HPTN 081 PSRT AE review to consider pause

^a Phone numbers and email addresses are found on the Protocol home page on the HVTN Members' site (<https://members.hvtn.org/protocols/hvtn703/HPTN081>).

^b HVTN CSS or HVTN Core designee

^c Does not include subjective reactogenicity symptoms (injection site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea, pruritus).

For all safety pauses, HVTN Core notifies the HVTN 703/HPTN 081 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN and HPTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the NIAID DSMB.

Once a trial is paused, the HVTN 703/HPTN 081 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of infusions is appropriate, consulting the NIAID DSMB if necessary. HVTN Core notifies the participating HVTN and HPTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study infusions. Based on the HVTN 703/HPTN 081 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 703/HPTN 081 PSRT notification or prompt HVTN 703/HPTN 081 PSRT AE review is triggered, HVTN Core notifies the HVTN 703/HPTN 081 PSRT as soon as possible during working hours (US Pacific Time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 703/HPTN 081 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and an applicable RE protocol-related safety information (such as IND safety reports, notification of study product holds due to the pause rules, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 703/HPTN 081 PSRT (see Section 10.4.2).

10.4 Review of cumulative safety data

Routine safety review occurs at the start of enrollment and then throughout the study.

Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and include queries to the CRSs. Events are tracked by internal reports until resolution.

10.4.1 Daily review

Blinded daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 703/HPTN 081 PSRT AE review criteria.

10.4.2 Biweekly review

During the infusion phase of the trial, the HVTN 703/HPTN 081 PSRT reviews clinical safety reports every 2 weeks and conducts calls to review the data as appropriate. After the infusions and the final postinfusion safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 703/HPTN 081 PSRT. The HVTN CSS or HVTN Core designee reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

10.4.3 DSMB review of cumulative safety data

The DSMB will periodically review accumulating safety data by masked treatment group. Prior to each such review, the SDMC will provide the DSMB with data as described in Section 4.7.1. Reports will be cumulative, generated from an up-to-date data file. Reports will show the data coded by treatment group; however, upon request of the DSMB, the SDMC will provide the Board with the actual treatment group.

10.5 Study termination

This study may be terminated early by NIAID upon recommendation by the DSMB, a pertinent national regulatory authority, Office for Human Research Protections (OHRP), or study product developer. In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

10.6 Social impact reporting

It is possible that participants' involvement in the study could result in social impacts. For example, a participant's involvement in the study could become known to others, and a social harm may result (ie, because participants could be perceived as being HIV infected or at "high risk" for HIV infection). Participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Alternatively, a social benefit may result (eg, a participant could feel good helping others).

Social harms are negative social impact events and social benefits are positive social impact events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. Social impacts will be collected and reported on CRFs during scheduled visits (see Appendix I through Appendix K). A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SSP. While maintaining participant confidentiality, study sites may engage their Community Advisory Board (CAB) in exploring the social context surrounding instances of social harms to minimize the potential occurrence of such an impact.

11 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with Good Clinical Practice (GCP) (ICHe6), the HVTN and HPTN network-specific *Manuals of Operations*, and DAIDS Clinical Research Policies and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Ancillary studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the SSP.

11.1 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site should contact the participant first, and then notify the IRB/EC and any applicable RE of the matter as soon as possible.

12 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of clinical trials. The HVTN and HPTN (hereafter, referred to as the “Networks”) have addressed ethical concerns in the following ways:

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for preventing HIV infection, using methods that are scientifically rigorous and valid, and in accordance with GCP guidelines.
- Network scientists and operational staff incorporate the philosophies underlying major codes [127-129], declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV prevention clinical trials.
- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. CABs are required by DAIDS and supported at all Network research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines.
- Network clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
- The Networks require that all international Network sites lacking national plans for providing ART develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants will be referred to programs for ART provision when the appropriate criteria for starting ART are met. If a program is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.
- The Networks agree that appropriate referrals for access to PrEP and PEP should be provided according to national and/or local guidelines.
- The Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.
- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.
- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.

- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.
- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.
- The Networks recognize the importance of institutional review and values the role of in country IRBs, ECs, and any applicable REs as custodians responsible for ensuring the ethical conduct of research in each setting.

13 IRB/EC/RE review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs to ensure that certain requirements are satisfied on initial and continuing review of research (Title 45, Code of Federal Regulations (CFR), Part 46.111(a) 1-7; 21 CFR 56.111(a) 1-7). The following section highlights how this protocol addresses each of these research requirements. Each Network Investigator welcomes IRB/EC and any applicable RE questions or concerns regarding these research requirements.

This trial is being conducted in Africa and North and South America, with partial funding from the US NIH. Due to this, the trial is subject to both US and local regulations and guidelines on the protection of human research subjects and ethical research conduct. Where there is a conflict in regulations or guidelines, the regulation or guideline providing the maximum protection of human research subjects will be followed.

In compliance with international and local (as appropriate) GCP, each research location has a locally based Principal Investigator (PI) who is qualified to conduct (and supervise the conduct of) the research; and the research addresses an important local health need for an HIV prevention method. In addition, the investigators take responsibility for the conduct of the study and the control of the study products, including obtaining all appropriate regulatory and ethical reviews of the research. Each participating site has a standard operating procedure for ensuring that participants have the necessary information to make a decision whether or not to consent to the research.

The sections below address each of the review concerns by IRBs/ECs and any applicable REs regarding how the research will be conducted.

13.1 Minimized risks to participants

45 CFR 46.111 (a) 1 and 21 CFR 56.111 (a) 1: Risks to subjects are minimized.

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants following study product administration and collecting information regarding side effects for several days following study product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product infusions, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use (for women); and (f) providing safety monitoring.

13.2 Reasonable risk/benefit balance

45 CFR 46.111(a) 2 and 21 CFR 56.111(a) 2: Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a healthy participant are not as apparent as they would be in treatment protocols, where a study participant may be ill and may have exhausted all conventional treatment options. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

13.3 Equitable subject selection

45 CFR 46.111 (a) 3 and 21 CFR 56.111 (a) 3: Subject selection is equitable

This protocol has specific inclusion and exclusion criteria for investigators to follow in admitting participants into the protocol. Participants are selected because of these criteria and not because of positions of vulnerability or privilege. Investigators are required to maintain screening and enrollment logs to document volunteers who screened into and out of the protocol and for what reasons.

13.4 Appropriate informed consent

45 CFR 46.111 (a) 4 & 5 and 21 CFR 56.111 (a) 4 & 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section 7.1). Each site is provided training in informed consent by the Networks as part of its entering the respective Network. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

13.5 Adequate safety monitoring

45 CFR 46.111 (a) 6 and 21 CFR 56.111 (a) 6: There is adequate provision for monitoring the data collected to ensure the safety of subjects.

This protocol has extensive safety monitoring in place (Section 10). Safety is monitored daily by the HVTN CSS or HVTN Core designee and routinely by the HVTN 703/HPTN 081 PSRT. In addition, a DSMB periodically reviews study data.

13.6 Protect privacy/confidentiality

45 CFR 46.111 (a) 7 and 21 CFR 56.111 (a) 7: There are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term "privacy" concerns research participants or potential research participants as individuals whereas the term "confidentiality" is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see Appendix A). The privacy of participants is protected by assigning unique identifiers in place of the participant's name on study data and specimens. In the United States, research participants in Network protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data/Specimens with the Networks and each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

14 Version history

The Protocol Team may modify the original version of the protocol. Modifications are made to Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 703/HPTN 081 are described below.

Protocol history and modifications

Date: August 11, 2015

Protocol version: 1.0

Protocol modification: NA

15 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at <http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf>.
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at <http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/>
- Division of AIDS Protocol Registration Manual. Available at <http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/prmanual.pdf>
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.0 [November 2014]. Available at <http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <http://rsc.tech-res.com/safetyandpharmacovigilance/manualforexpeditedreporting.aspx>
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 703/HPTN 081 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 703/HPTN 081 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN Laboratory Manual of Operations. Accessible through the HVTN website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/publications/dgr/Pages/index.aspx>.
- HVTN Lab assay algorithm
- HVTN algorithm for diagnosis of HIV infections. Part of the HVTN Site Lab Reference Manual (see above).

- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>
- HVTN 703/HPTN 081 Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.
- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>.
- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at https://phacs.nichdclinicalstudies.org/publicDocs/DAIDS_SourceDocPolicy.pdf
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

See Section 17 for literature cited in the background and statistics sections of this protocol.

16 Acronyms and abbreviations

Ab	antibody
Ad	adenovirus
ACASI	audio computer assisted self-interview
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADCVI	antibody-dependent cellular viral inhibition
AIA	anti-idiotypic antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
BLI	BioLayer Interferometry
BMI	body mass index
bNab	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHO	Chinese hamster ovary
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence intervals
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CRS*	clinical research site
DAERS	DAIDS Adverse Event Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DNA	deoxyribonucleic acid
DSMB	(NIAID) Data and Safety Monitoring Board
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EC ₅₀	effective concentration (50%)
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration

FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
GC	gonorrhea
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hgb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPTN	HIV Prevention Trials Network
HRMS	high resolution mass spectrometric
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
IC ₅₀	inhibitory concentration (50%)
ICH	International Conference on Harmonisation
ICF	informed consent form
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IPEC	Instituto de Pesquisa Clinica Evandro Chagas
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LANL	Los Alamos National Laboratory
LC	Laboratory Center
LOC	Leadership and Operations Center
mAb	monoclonal antibody
MITT	modified intent-to-treat
MOP	Manual of Operations
MPER	membrane proximal external region
MSM	men who have sex with men
MTF	male-to-female
nAb	neutralizing antibody
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NICD	National Institute for Communicable Diseases (Johannesburg, South Africa)
NIH	US National Institutes of Health
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NVITAL	NIAID Vaccine Immune T-Cell Antibody Laboratory
OBA	NIH Office of Biotechnology Activities

OC	Oversight Committee
OHRP	US Office for Human Research Protections
PAB	DAIDS Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PE	prevention efficacy
PEP	postexposure prophylaxis
PI	Principal Investigator
PK	pharmacokinetic
PMTCT	prevention of mother-to-child (HIV) transmission
PNG	potential N-linked glycosylation
PrEP	pre-exposure prophylaxis
PSP	Prevention Sciences Program
PSRT	Protocol Safety Review Team
PYR	person year
RAB	DAIDS Regulatory Affairs Branch
RAC	NIH Recombinant DNA Advisory Committee
RE	regulatory entity
RPR	rapid plasma reagin
RSC	(DAIDS) Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SIV	simian immunodeficiency virus
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study specific procedures
STI	sexually transmitted infection
TasP	treatment as prevention
TCID ₅₀	tissue culture infectious dose (50%)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TG	transgender
tMLE	targeted maximum likelihood estimation
TPP	target product profile
TTNI	time to target number of infections
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VISP	Vaccine induced seropositivity

VRC Vaccine Research Center (NIAID)
VRP Vaccine Research Program
WHO World Health Organization

* CRSs were formerly referred to as HIV Vaccine Trial Units (HVTUs). Conversion to use of the term CRS is in process, and some HVTN documents may still refer to HVTUs.

17 Literature cited

1. UNAIDS. Report on the Global AIDS Epidemic, 2012 country progress reports. <http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/>. 2013. Last accessed: 2-20-2013
2. UNAIDS. Global Report: Report on the global AIDS epidemic 2013. **2013**;UNAIDS / JC2502/1/E.
3. WHO in partnership with UNICEF and UNAIDS. Global Report on HIV Treatment 2013: Results, Impact and Opportunities. **2014**.
4. UNAIDS. Local Epidemics Issues Brief. **2014**.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de BG, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **2011**;365:493-505.
6. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* **2010**;363:2587-99.
7. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: Limitations to Treatment Safety and Efficacy: Adverse Effects of Antiretroviral Agents. <http://aidsinfo.nih.gov/guidelines>. 5-1-2014. Last accessed: 2-17-2015
8. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* **2012**;26:F13-F19.
9. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clin Infect Dis* **1992**;14:580-6.
10. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2006**;55:1-23.
11. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. *Curr Opin HIV AIDS* **2015**;10:129-34.
12. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* **1998**;102:531-7.

13. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, Connor EM, Losonsky GA. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics* **2010**;125:e35-e51.
14. Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective. *Int J Pediatr* **2014**;2014:571609.
15. Li Y, Migueles SA, Welcher B, Svehla K, Phogat A, Louder MK, Wu X, Shaw GM, Connors M, Wyatt RT, Mascola JR. Broad HIV-1 neutralization mediated by CD4-binding site antibodies. *Nat Med* **2007**;13:1032-4.
16. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarragona-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee DA, Manigart O, Karita E, Inwoley A, Jaoko W, Dehovitz J, Bekker LG, Pitisuttithum P, Paris R, Walker LM, Poignard P, Wrin T, Fast PE, Burton DR, Koff WC. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. *J Virol* **2009**;83:7337-48.
17. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, McKee K, O'Dell S, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science* **2010**;329:856-61.
18. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, Kwon YD, Scheid JF, Shi W, Xu L, Yang Y, Zhu J, Nussenzweig MC, Sodroski J, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science* **2010**;329:811-7.
19. Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, Wibmer CK, Puren A, DeCamp A, Gilbert PB, Wood B, Montefiori DC, Binley JM, Shaw GM, Haynes BF, Mascola JR, Morris L. Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. *J Virol* **2009**;83:8925-37.
20. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol* **2011**;85:4828-40.
21. Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez BM, Silacci C, Pinna D, Jarrossay D, Balla-Jhaghoorsingh S, Willems B, Zekveld MJ, Dreja H, O'Sullivan E, Pade C, Orkin C, Jeffs SA, Montefiori DC, Davis D, Weissenhorn W, McKnight A, Heeney JL, Sallusto F, Sattentau QJ, Weiss RA, Lanzavecchia A. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. *PLoS ONE* **2010**;5:e8805.
22. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, Wang SK, Ramos A, Chan-Hui PY, Moyle M, Mitcham JL, Hammond PW, Olsen OA, Phung P, Fling S, Wong CH, Phogat S, Wrin T, Simek MD, Koff WC, Wilson IA, Burton DR, Poignard

- P. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* **2011**;477:466-70.
23. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, Pietzsch J, Fenyo D, Abadir A, Velinzon K, Hurley A, Myung S, Boulad F, Poignard P, Burton DR, Pereyra F, Ho DD, Walker BD, Seaman MS, Bjorkman PJ, Chait BT, Nussenzweig MC. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science* **2011**;333:1633-7.
24. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, Wood B, Nathe C, Richman D, Tomaras GD, Bibollet-Ruche F, Robinson JE, Morris L, Shaw GM, Montefiori DC, Mascola JR. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. *J Virol* **2008**;82:11651-68.
25. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, Stamatatos L. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. *J Virol* **2009**;83:757-69.
26. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, Wu X, Seaman MS, Wrin T, Kwong PD, Wyatt RT, Mascola JR, Poignard P, Burton DR. PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. *J Virol* **2012**;86:4394-403.
27. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL, Lehrman JK, Priddy FH, Olsen OA, Frey SM, Hammond PW, Kaminsky S, Zamb T, Moyle M, Koff WC, Poignard P, Burton DR. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science* **2009**;326:285-9.
28. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, Phogat SK, Poignard P, Burton DR. A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. *PLoS Pathog* **2010**;6:e1001028.
29. McLellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, Louder R, Pejchal R, Sastry M, Dai K, O'Dell S, Patel N, Shahzad-ul-Hussan S, Yang Y, Zhang B, Zhou T, Zhu J, Boyington JC, Chuang GY, Diwanji D, Georgiev I, Kwon YD, Lee D, Louder MK, Moquin S, Schmidt SD, Yang ZY, Bonsignori M, Crump JA, Kapiga SH, Sam NE, Haynes BF, Burton DR, Koff WC, Walker LM, Phogat S, Wyatt R, Orwenyo J, Wang LX, Arthos J, Bewley CA, Mascola JR, Nabel GJ, Schief WR, Ward AB, Wilson IA, Kwong PD. Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature* **2011**;480:336-43.
30. Kong L, Lee JH, Doores KJ, Murin CD, Julien JP, McBride R, Liu Y, Marozsan A, Cupo A, Klasse PJ, Hoffenberg S, Caulfield M, King CR, Hua Y, Le KM, Khayat R, Deller MC, Clayton T, Tien H, Feizi T, Sanders RW, Paulson JC, Moore JP, Stanfield RL, Burton DR, Ward AB, Wilson IA. Supersite of immune vulnerability on the glycosylated face of HIV-1 envelope glycoprotein gp120. *Nat Struct Mol Biol* **2013**;20:796-803.

31. Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, Imamichi H, Bailer RT, Chakrabarti B, Sharma SK, Alam SM, Wang T, Yang Y, Zhang B, Migueles SA, Wyatt R, Haynes BF, Kwong PD, Mascola JR, Connors M. Broad and potent neutralization of HIV-1 by a gp41-specific human antibody. *Nature* **2012**;491:406-12.
32. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat Med* **2009**;15:866-70.
33. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. *Curr Opin Immunol* **2010**;22:358-66.
34. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, Kaufmann DE, McElrath MJ, Nussenzweig MC, Pulendran B, Scanlan CN, Schief WR, Silvestri G, Streeck H, Walker BD, Walker LM, Ward AB, Wilson IA, Wyatt R. A Blueprint for HIV Vaccine Discovery. *Cell Host Microbe* **2012**;12:396-407.
35. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. *Proc Natl Acad Sci U S A* **2005**;102:14943-8.
36. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **2012**;37:412-25.
37. Georgiev IS, Gordon JM, Zhou T, Kwong PD. Elicitation of HIV-1-neutralizing antibodies against the CD4-binding site. *Curr Opin HIV AIDS* **2013**;8:382-92.
38. Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, Imamichi H, Doria-Rose N, Hoxie JA, Connors M, Shaw GM, Wyatt RT, Mascola JR. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol* **2012**;86:5844-56.
39. Shibata R, Igarashi T, Haigwood N, Buckler-White A, Ogert R, Ross W, Willey R, Cho MW, Martin MA. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat Med* **1999**;5:204-10.
40. Baba TW, Liska V, Hofmann-Lehmann R, Vlasak J, Xu W, Ayehunie S, Cavacini LA, Posner MR, Katinger H, Stiegler G, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Lu Y, Wright JE, Chou TC, Ruprecht RM. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat Med* **2000**;6:200-6.
41. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Jiang S, Li PL, Baba TW, Montefiori DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Ruprecht RM. Postnatal pre- and postexposure passive immunization strategies: protection of neonatal macaques against oral simian-human immunodeficiency virus challenge. *J Med Primatol* **2002**;31:109-19.
42. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.

43. Hessel AJ, Rakasz EG, Poignard P, Hangartner L, Landucci G, Forthal DN, Koff WC, Watkins DI, Burton DR. Broadly neutralizing human anti-HIV antibody 2G12 is effective in protection against mucosal SHIV challenge even at low serum neutralizing titers. *PLoS Pathog* **2009**;5:e1000433.
44. Hessel AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nat Med* **2009**;15:951-4.
45. Moldt B, Rakasz EG, Schultz N, Chan-Hui PY, Swiderek K, Weisgrau KL, Piaskowski SM, Bergman Z, Watkins DI, Poignard P, Burton DR. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. *Proc Natl Acad Sci U S A* **2012**;109:18921-5.
46. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, McKee K, Kong WP, Shi W, Chen X, Todd JP, Letvin NL, Huang J, Nason MC, Hoxie JA, Kwong PD, Connors M, Rao SS, Mascola JR, Nabel GJ. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. *Sci Transl Med* **2014**;6:243ra88.
47. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, Zeng M, Schmidt SD, Todd JP, Penzak SR, Saunders KO, Nason MC, Haase AT, Rao SS, Blumberg RS, Mascola JR, Nabel GJ. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature* **2014**;514:642-5.
48. Rudicell RS, Kwon YD, Ko SY, Pegu A, Louder MK, Georgiev IS, Wu X, Zhu J, Boyington JC, Chen X, Shi W, Yang ZY, Doria-Rose NA, McKee K, O'Dell S, Schmidt SD, Chuang GY, Druz A, Soto C, Yang Y, Zhang B, Zhou T, Todd JP, Lloyd KE, Eudailey J, Roberts KE, Donald BR, Bailer RT, Ledgerwood J, Mullikin JC, Shapiro L, Koup RA, Graham BS, Nason MC, Connors M, Haynes BF, Rao SS, Roederer M, Kwong PD, Mascola JR, Nabel GJ. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* **2014**;88:12669-82.
49. Florese RH, Demberg T, Xiao P, Kuller L, Larsen K, Summers LE, Venzon D, Cafaro A, Ensoli B, Robert-Guroff M. Contribution of nonneutralizing vaccine-elicited antibody activities to improved protective efficacy in rhesus macaques immunized with Tat/Env compared with multigenic vaccines. *J Immunol* **2009**;182:3718-27.
50. Forthal DN, Landucci G, Phan TB, Becerra J. Interactions between natural killer cells and antibody Fc result in enhanced antibody neutralization of human immunodeficiency virus type 1. *J Virol* **2005**;79:2042-9.
51. Asmal M, Sun Y, Lane S, Yeh W, Schmidt SD, Mascola JR, Letvin NL. Antibody-dependent cell-mediated viral inhibition emerges after simian immunodeficiency virus SIVmac251 infection of rhesus monkeys coincident with gp140-binding antibodies and is effective against neutralization-resistant viruses. *J Virol* **2011**;85:5465-75.
52. Tudor D, Derrien M, Diomedes L, Drillet AS, Houimel M, Moog C, Reynes JM, Lopalco L, Bomsel M. HIV-1 gp41-specific monoclonal mucosal IgAs derived from highly exposed but IgG-seronegative individuals block HIV-1 epithelial transcytosis and

neutralize CD4(+) cell infection: an IgA gene and functional analysis. *Mucosal Immunol* **2009**;2:412-26.

53. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, Shapiro L, Mascola JR. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature* **2014**;509:55-62.
54. Pancera M, Shahzad-ul-Hussan S, Doria-Rose NA, McLellan JS, Bailer RT, Dai K, Loesgen S, Louder MK, Staupe RP, Yang Y, Zhang B, Parks R, Eudailey J, Lloyd KE, Blinn J, Alam SM, Haynes BF, Amin MN, Wang LX, Burton DR, Koff WC, Nabel GJ, Mascola JR, Bewley CA, Kwong PD. Structural basis for diverse N-glycan recognition by HIV-1-neutralizing V1-V2-directed antibody PG16. *Nat Struct Mol Biol* **2013**;20:804-13.
55. Zhou T, Lynch RM, Chen L, Acharya P, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, McKee K, O'Dell S, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, Peng HP, Yang AS, Mullikin JC, Gray MD, Stamatatos L, Burton DR, Koff WC, Cohen MS, Haynes BF, Casazza JP, Connors M, Corti D, Lanzavecchia A, Sattentau QJ, Weiss RA, West AP, Jr., Bjorkman PJ, Scheid JF, Nussenzweig MC, Shapiro L, Mascola JR, Kwong PD. Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors. *Cell* **2015**;161:1280-92.
56. Chuang GY, Acharya P, Schmidt SD, Yang Y, Louder MK, Zhou T, Kwon YD, Pancera M, Bailer RT, Doria-Rose NA, Nussenzweig MC, Mascola JR, Kwong PD, Georgiev IS. Residue-level prediction of HIV-1 antibody epitopes based on neutralization of diverse viral strains. *J Virol* **2013**;87:10047-58.
57. Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, Denham SA, Heil ML, Kasolo F, Musonda R, Hahn BH, Shaw GM, Korber BT, Allen S, Hunter E. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* **2004**;303:2019-22.
58. Wilen CB, Parrish NF, Pfaff JM, Decker JM, Henning EA, Haim H, Petersen JE, Wojcechowskyj JA, Sodroski J, Haynes BF, Montefiori DC, Tilton JC, Shaw GM, Hahn BH, Doms RW. Phenotypic and immunologic comparison of clade B transmitted/founder and chronic HIV-1 envelope glycoproteins. *J Virol* **2011**;85:8514-27.
59. Hall HI, Song R, Rhodes P, Prejean J, An Q, Lee LM, Karon J, Brookmeyer R, Kaplan EH, McKenna MT, Janssen RS. Estimation of HIV incidence in the United States. *JAMA* **2008**;300:520-9.
60. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, Lin LS, An Q, Mermin J, Lansky A, Hall HI. Estimated HIV incidence in the United States, 2006-2009. *PLoS ONE* **2011**;6:e17502.

61. Centers for Disease Control and Prevention. Diagnosis of HIV infection in the United States and dependent areas, 2013. HIV Surveillance Report, 2013; Vol. 25. <http://www.cdc.gov/hiv/library/reports/surveillance/>. 2015. Last accessed: 5-13-2015
62. Centers for Disease Control and Prevention. Estimates HIV incidence in the United States, 2007-2010. HIV Surveillance Supplemental Report 2012;17(No. 4). <http://www.cdc.gov/hiv/topics/surveillance/resources/reports/#supplemental>. 12-2-2015. Last accessed: 5-13-2015
63. Koblin BA, Mayer KH, Eshleman SH, Wang L, Mannheimer S, Del RC, Shoptaw S, Magnus M, Buchbinder S, Wilton L, Liu TY, Cummings V, Piwowar-Manning E, Fields SD, Griffith S, Elharrar V, Wheeler D. Correlates of HIV acquisition in a cohort of Black men who have sex with men in the United States: HIV prevention trials network (HPTN) 061. PLoS ONE **2013**;8:e70413.
64. Sullivan PS, Peterson J, Rosenberg ES, Kelley CF, Cooper H, Vaughan A, Salazar LF, Frew P, Wingood G, Diclemente R, Del RC, Mulligan M, Sanchez TH. Understanding racial HIV/STI disparities in black and white men who have sex with men: a multilevel approach. PLoS ONE **2014**;9:e90514.
65. UNAIDS. The GAP Report. **2014**.
66. Padian NS, van der SA, Ramjee G, Chipato T, de Bruyn G, Blanchard K, Shiboski S, Montgomery ET, Fancher H, Cheng H, Rosenblum M, van der LM, Jewell N, McIntyre J. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. Lancet **2007**;370:251-61.
67. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, Cowan F, Casapia M, Ortiz A, Fuchs J, Buchbinder S, Koblin B, Zwierski S, Rose S, Wang J, Corey L. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. Lancet **2008**;371:2109-19.
68. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, Nchabeleng M, Mlisana K, Metch B, de BG, Latka MH, Roux S, Mathebula M, Naicker N, Ducar C, Carter DK, Puren A, Eaton N, McElrath MJ, Robertson M, Corey L, Kublin JG. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. Lancet Infect Dis **2011**;11:507-15.
69. Gray GE, Moodie Z, Metch B, Gilbert PB, Bekker LG, Churchyard G, Nchabeleng M, Mlisana K, Laher F, Roux S, Mngadi K, Innes C, Mathebula M, Allen M, McElrath MJ, Robertson M, Kublin J, Corey L. Recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up of the phase 2b HVTN 503/Phambili study. Lancet Infect Dis **2014**;14:388-96.
70. Abdool KQ, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, Kharsany AB, Sibeko S, Mlisana KP, Omar Z, Gengiah TN, Maarschalk S, Arulappan N, Mlotshwa M, Morris L, Taylor D. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science **2010**;329:1168-74.

71. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2012**;367:411-22.
72. NIAID. Daily-Use HIV Prevention Approaches Prove Ineffective Among Women in NIH Study. <http://www.niaid.nih.gov/news/newsreleases/2013/Pages/VOICEwomen.aspx>. 3-4-2013
73. World Medical Association. Ethical Principles for Medical Research Involving Human Subjects, Note of Clarification on Paragraph 29. **2002**.
74. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* **2000**;283:2701-11.
75. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. *N Engl J Med* **2001**;345:915-9.
76. Ng CT, Jaworski JP, Jayaraman P, Sutton WF, Delio P, Kuller L, Anderson D, Landucci G, Richardson BA, Burton DR, Forthal DN, Haigwood NL. Passive neutralizing antibody controls SHIV viremia and enhances B cell responses in infant macaques. *Nat Med* **2010**;16:1117-9.
77. Lynch RM, Wong P, Tran L, O'Dell S, Nason MC, Li Y, Wu X, Mascola JR. HIV-1 fitness cost associated with escape from the VRC01 class of CD4 binding site neutralizing antibodies. *J Virol* **2015**;89:4201-13.
78. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials* **2010**;7:197-208.
79. Gilbert PB, Grove D, Gabriel E, Huang Y, Gray G, Hammer SM, Buchbinder SP, Kublin J, Corey L, Self SG. A Sequential Phase 2b Trial Design for Evaluating Vaccine Efficacy and Immune Correlates for Multiple HIV Vaccine Regimens. *Stat Commun Infect Dis* **2011**;3.
80. McCormack S, Dunn D. Pragmatic open-label randomized trial of preexposure prophylaxis: The PROUD study (Abstract 22LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
81. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On demand PrEP with Oral TDF-FTC in MSM: Results of the ANRS Ipergay trial (Abstract 23LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
82. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* **2012**;367:423-34.

83. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E, Twesigye R, Ngure K, Apaka C, Tamooch H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* **2012**;367:399-410.
84. Rees, H, Delany-Moretlwa, S, Baron, D, Lombard, C, Gray, G, Myers, L, Panchia, R, Schwartz, J, and Doncel, G. FACTS 001 Phase III trial of pericoital Tenofovir 1% gel for HIV prevention in women (Abstract 26LB).
<http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women>. 2015. Last accessed: 6-15-2015
85. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodhi N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Masse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2015**;372:509-18.
86. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, Cohen MS, Kashuba AD. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med* **2011**;3:112re4.
87. Centers for Disease Control and Prevention. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex With Men.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm>. 1-28-2011. Last accessed: 4-10-2015
88. World Health Organization. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. July 2012. **2012**.
89. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: A Clinical Practice Guideline. **2014**.
90. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: Clinical Providers' Supplement. 2014. US Centers for Disease Control and Prevention.
91. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach.
<http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>. 6-30-2013. Last accessed: 2-2-2015
92. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, Gupta S, Herzyk D, Hurst C, Ivens IA, Kawabata T, Maier C, Mounho B, Rup B, Shankar G, Smith H, Thomas P, Wierda D. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol* **2009**;54:164-82.

93. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* **2004**;93:2645-68.
94. Li Y, O'Dell S, Walker LM, Wu X, Guenaga J, Feng Y, Schmidt SD, McKee K, Louder MK, Ledgerwood JE, Graham BS, Haynes BF, Burton DR, Wyatt RT, Mascola JR. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *J Virol* **2011**;85:8954-67.
95. Haynes BF, Fleming J, St Clair EW, Katinger H, Stiegler G, Kunert R, Robinson J, Searce RM, Plonk K, Staats HF, Ortel TL, Liao HX, Alam SM. Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* **2005**;308:1906-8.
96. Mascola JR, Lewis MG, Stiegler G, Harris D, VanCott TC, Hayes D, Louder MK, Brown CR, Sapan CV, Frankel SS, Lu Y, Robb ML, Katinger H, Birx DL. Protection of Macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol* **1999**;73:4009-18.
97. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, Beary H, Hayes D, Frankel SS, Birx DL, Lewis MG. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat Med* **2000**;6:207-10.
98. Mascola JR. Defining the protective antibody response for HIV-1. *Curr Mol Med* **2003**;3:209-16.
99. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
100. Parren PW, Marx PA, Hessel AJ, Luckay A, Harouse J, Cheng-Mayer C, Moore JP, Burton DR. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* **2001**;75:8340-7.
101. Sadjadpour R, Donau OK, Shingai M, Buckler-White A, Kao S, Strebel K, Nishimura Y, Martin MA. Emergence of gp120 V3 variants confers neutralization resistance in an R5 simian-human immunodeficiency virus-infected macaque elite neutralizer that targets the N332 glycan of the human immunodeficiency virus type 1 envelope glycoprotein. *J Virol* **2013**;87:8798-804.
102. Gautam R, Nishimura Y, Lee WR, Donau O, Buckler-White A, Shingai M, Sadjadpour R, Schmidt SD, LaBranche CC, Keele BF, Montefiori D, Mascola JR, Martin MA. Pathogenicity and mucosal transmissibility of the R5-tropic simian/human immunodeficiency virus SHIV(AD8) in rhesus macaques: implications for use in vaccine studies. *J Virol* **2012**;86:8516-26.
103. Shingai M, Donau OK, Plishka RJ, Buckler-White A, Mascola JR, Nabel GJ, Nason MC, Montefiori D, Moldt B, Poignard P, Diskin R, Bjorkman PJ, Eckhaus MA, Klein F, Mouquet H, Cetrulo Lorenzi JC, Gazumyan A, Burton DR, Nussenzweig MC, Martin MA, Nishimura Y. Passive transfer of modest titers of potent and broadly neutralizing

anti-HIV monoclonal antibodies block SHIV infection in macaques. *J Exp Med* **2014**;211:2061-74.

104. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* **2010**;9:325-38.
105. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol* **2009**;5:499-521.
106. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* **2010**;14:E10-E21.
107. Rosenbaum P. The consequences of adjustment for a concomitant variable that has been affected by the treatment. *Journal of the Royal Statistical Society, Series A (General)* **1984**;147:656-66.
108. Joffe MM, Greene T. Related causal frameworks for surrogate outcomes. *Biometrics* **2009**;65:530-8.
109. Follmann D. Augmented designs to assess immune response in vaccine trials. *Biometrics* **2006**;62:1161-9.
110. Gilbert PB, Hudgens MG. Evaluating candidate principal surrogate endpoints. *Biometrics* **2008**;64:1146-54.
111. Huang Y, Gilbert PB, Wolfson J. Design and estimation for evaluating principal surrogate markers in vaccine trials. *Biometrics* **2013**;69:301-9.
112. Rida W, Fast P, Hoff R, Fleming T. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol* **1997**;16:195-203.
113. Juraska, M, Grove, D, Yu, X, and Gilbert, PG. seqDesign: Simulation and Group Sequential Monitoring of Randomized Two-Stage Treatment Efficacy Trials with Time-to-Event Endpoints. R package version 1.1. <http://CRAN.R-project.org?package=seqDesign>. 4-27-2015. Last accessed: 5-15-2015
114. Berger RL, Boos DD. P values maximized over a confidence set for the nuisance parameter. *Journal of the American Statistical Association* **1994**;89:1012-6.
115. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* **2013**;369:2083-92.
116. Fogel JM, Wang L, Parsons TL, Ou SS, Piwowar-Manning E, Chen Y, Mudhune VO, Hosseinipour MC, Kumwenda J, Hakim JG, Chariyalertsak S, Panchia R, Sanne I, Kumarasamy N, Grinsztejn B, Makhema J, Pilotto J, Santos BR, Mayer KH, McCauley M, Gamble T, Bumpus NN, Hendrix CW, Cohen MS, Eshleman SH. Undisclosed

antiretroviral drug use in a multinational clinical trial (HIV Prevention Trials Network 052). *J Infect Dis* **2013**;208:1624-8.

117. Marzinke MA, Clarke W, Wang L, Cummings V, Liu TY, Piwowar-Manning E, Breaud A, Griffith S, Buchbinder S, Shoptaw S, Del RC, Magnus M, Mannheimer S, Fields SD, Mayer KH, Wheeler DP, Koblin BA, Eshleman SH, Fogel JM. Nondisclosure of HIV status in a clinical trial setting: antiretroviral drug screening can help distinguish between newly diagnosed and previously diagnosed HIV infection. *Clin Infect Dis* **2014**;58:117-20.
118. Chen I, Connor MB, Clarke W, Marzinke MA, Cummings V, Breaud A, Fogel JM, Laeyendecker O, Fields SD, Donnell D, Griffith S, Scott HM, Shoptaw S, Del RC, Magnus M, Mannheimer S, Wheeler DP, Mayer KH, Koblin BA, Eshleman SH. Antiretroviral Drug Use and HIV Drug Resistance Among HIV-Infected Black Men Who Have Sex With Men: HIV Prevention Trials Network 061. *J Acquir Immune Defic Syndr* **2015**;69:446-52.
119. Chen I, Clarke W, Ou S, Marzinke M, Breaud A, Hughes J, Richardson P, Haley D, Adimora A, Golin C, del Rio C, Kuo I, Mannhaimer S, Soto-Torres L, Rompalo A, Justman J, Hodder S, Eshleman S. Antiretroviral drug use in a cohort of HIV-uninfected women in the United States . 8th IAS Conference on HIV Pathogenesis, Treatment, and Prevention, Vancouver, Canada, July 19-22, **2015**
120. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data* (Second Edition). John Wiley & Sons, Inc., **2002**.
121. Moore K, van der Laan M. Application of time-to-event methods in the assessment of safety in clinical trials. U. C. Berkeley Division of Biostatistics Working Paper Series, Paper 248. 2009.
122. van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. Springer, **2011**.
123. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, Sinangil F, D'Souza P, Rodriguez-Chavez IR, DeCamp A, Giganti M, Berman PW, Self SG, Montefiori DC. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. *J Infect Dis* **2010**;202:595-605.
124. Montefiori DC. Measuring HIV neutralization in a luciferase reporter gene assay. *Methods Mol Biol* **2009**;485:395-405.
125. Todd CA, Greene KM, Yu X, Ozaki DA, Gao H, Huang Y, Wang M, Li G, Brown R, Wood B, D'Souza MP, Gilbert P, Montefiori DC, Sarzotti-Kelsoe M. Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells. *J Immunol Methods* **2012**;375:57-67.
126. Ozaki DA, Gao H, Todd CA, Greene KM, Montefiori DC, Sarzotti-Kelsoe M. International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials. *PLoS ONE* **2012**;7:e30963.
127. UNAIDS. *Ethical considerations in biomedical HIV prevention trials*. **2007**.

128. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. **1979.**
129. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics **2002**;17-23.

Appendix A Sample informed consent form

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

Protocol number: HVTN 703/HPTN 081, The AMP Study

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test the antibody called VRC01 against HIV. HIV is the virus that causes AIDS. Antibodies are one of the natural ways the body fights infection. Researchers can also make antibodies in laboratories and give them to people intravenously (with an IV). We will tell you more about this procedure below. This has been done successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 3900 people will take part in this study at multiple sites in Africa and North and South America. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

1. We are doing this study to answer several questions.

- Is the antibody safe to give to people?
- Are people able to take the antibody without becoming too uncomfortable?
- Does the antibody lower people's chances of getting infected with HIV?
- If the antibody does lower people's chances of getting infected with HIV, how much of it is needed to provide protection from HIV?

2. The antibody cannot give you HIV.

It is impossible for the antibody to give you HIV. Also, it cannot cause you to give HIV to someone else. However, we do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. The antibody is experimental.

The antibody being tested is called VRC-HIVMAB060-00-AB. It is an antibody against the HIV virus. From here on, we will call it VRC01 or the antibody. This is an experimental product. That means we do not know whether the antibody will be safe to use in people, or whether it will work to prevent HIV infection. This antibody is used only in research studies.

VRC01 was developed by the Vaccine Research Center at the US National Institutes of Health (NIH).

In laboratory and animal studies, VRC01 attached to and prevented infection by many strains of HIV viruses from around the world. We do not know if the antibody will prevent HIV infection when given to people. This study is designed to help us answer that question.

Risks of VRC01 antibody:

There have been 3 studies using the antibody in people in the United States at the NIH Clinical Center and at HVTN clinics. As of May 2015, over 100 people received the antibody or placebo (a liquid with no antibody in it). The antibody has been tested in one study with HIV-positive people and in 2 studies with HIV-negative people. So far, it has not made them too uncomfortable or caused serious health problems. One participant had chest discomfort and one had a rash. These participants might have gotten the antibody or the placebo. To be safe, no more antibody or placebo was given to these participants. Some participants have had mild body discomfort, muscle, or joint pain after getting the VRC01 antibody.

VRC01 may have other side effects that we do not know about yet.

General risks of antibodies:

Antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain.

Rarely, some antibodies have caused serious reactions. These reactions may be life-threatening. Please tell us if you have ever had any of the following reactions.

- One type of serious reaction may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face.
- A second type of serious reaction may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath.

Rarely, antibodies licensed for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with the VRC01 antibody.

When antibodies are given to a person by IV they do not last in the body more than a few months. Any antibody given to you in this study should be gone from your body several months after your last dose.

Joining the study

4. It is completely up to you whether or not to join the study.

Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

If you join this study, you may not be allowed to join some other kinds of HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you receive a study product. Also during the study, you should not donate blood or tissue.

If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. If you decide to join the study, we will screen you to see if you are eligible.

Screening involves a physical exam, HIV test and health history. A physical exam may include, but is not limited to:

- Checking your weight, temperature and blood pressure
- Looking in your mouth and throat
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV. If you could become pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

(Sites: adapt the following section so it is applicable to the care available at your site)

6. If we find that you have a health problem during screening or during the study:

- We will tell you about the care that we can give here for free.
- For the care that we cannot give, we will explain how we will help link you to care elsewhere.

For health problems that are unrelated to the study, we will not pay for medical costs.

7. If you could become pregnant, you must agree to use birth control to join this study.

Site: List approved birth control methods here if you do not want to hand out the separate Approved Birth Control Methods sheets provided in Appendices B and C.

You should not become pregnant during the study because we do not know how the antibody could affect the developing baby. You must agree to use effective birth control from 21 days before you first receive the antibody until your last scheduled clinic visit (about 1¾ years after your first IV). We will talk to you about effective birth control methods. They are listed on a handout that we will give to you. *Site: Delete the preceding sentence if you include the birth control sheet in this consent form.* If you join the study, we will test you for pregnancy at some visits, including before each study IV.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. You will come to the clinic for scheduled visits about [#] times over [#] months.

The study will require [#] visits. That is 1 visit every 4 weeks. You may have to come for more visits if you have a lab or health issue.

Visits can last from about [#] minutes to [#] hours. The IV procedure takes about 30 to 60 minutes.

We may contact you after the main study ends (for example, to tell you about the study results).

9. We will give you [Site: Insert compensation] for each study visit you complete.

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, birth control costs for female participants who could become pregnant).

Following paragraph for US sites only:

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

You do not have to pay anything to be in this study.

10. We will give you either the antibody or a placebo.

Not everyone in this study will get the VRC01 antibody. Some people will get a placebo, a substance that does not contain any antibody. We will compare the results from people who got the placebo with results from people who got the VRC01 antibody. In this study, the placebo is sterile salt water, which is found naturally in the body.

There are six groups in this study. Three groups are for participants from North and South America and three groups are for participants from Africa. In each region, one group will get a lower dose of the VRC01 antibody, one group will get a higher dose, and one group will get the placebo. The high and low doses of the antibody will be adjusted for your body weight. We will weigh you to determine the amount you will get.

Overall, if you join this study, you have a 2-in-3 chance of receiving the study antibody.

Site: Modify the randomization metaphor in the next sentence as appropriate to your local culture.

Whether you get the low dose of the antibody, the high dose of the antibody, or the placebo is completely random, like flipping a coin.

We have no say in whether you get the antibody or the placebo. If you get the antibody, we have no say in which dose you get. We will not know what you are getting, and neither will you. Only the pharmacist at your site will have this information while the study is going on.

You will have to wait until everyone completes their final study visits to find out whether you got the antibody or the placebo. This could be up to about 5 years. But, if you have a serious medical problem and need to know what you got before the end of the study, we can tell you.

If it is found to be effective, there are no plans to give the antibody to participants after the study. Instead, we will use what is learned in this study to determine if the antibody would be useful to prevent HIV, how the antibody could be improved, and how to produce it for wide public use.

11. We will give you the antibody or placebo on a schedule.

You will get the VRC01 antibody or the placebo during the study by IV. A needle is placed into a vein in your arm. The needle is connected by a small tube to a small bag of fluid that contains the antibody or placebo. An IV pump controls how fast the fluid drips from the bag, through the tube, and into your vein. There will be 10 IV procedures, one IV every 8 weeks. Other study visits will not include IVs.

Infusion schedule



Group	Dose	First IV	Weeks after first IV								
			Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72
Groups 1 and 4	Lower dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Groups 2 and 5	Higher dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Groups 3 and 6	Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

You will have to wait in the clinic for about 30 minutes after the first IV to see if there are any problems. You probably will not have to wait after the IVs at the rest of the IV visits. After each IV visit, for that night and for three more days, you will be asked to record how you feel. To help you do this, we can give you tools and show you how to use them. We will ask you the ways we can contact you. We will contact you about 3 days after each IV visit to ask how you have been feeling.

12. In addition to giving you the antibody or placebo, we will:

- Perform regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Perform physical exams;
- Perform pregnancy tests if you could become pregnant;
- Ask questions about your health, including medications you may be taking;
- Ask questions about any personal problems or benefits you may have from being in the study; and
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 160 mL (2 teaspoons to $\frac{2}{3}$ cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, “To compare, people who donate blood in the US can give a total of about 500 mL in an 8-week period.”). Modify the example for cultural relevance and alter blood volumes as necessary.

Site: Insert Appendix E, Table of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.

We will be looking for side effects.

We will also do tests for the following infections: syphilis, gonorrhea, chlamydia, and trichomonas. We will explain what each of these infections is. If the tests say you have an infection, we will provide counseling and will help you get treatment. This study cannot pay for that treatment. *[Site: Revise preceding sentence if you provide or pay for STI treatment.]*

We will review the results of the procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. We will test your samples for this study.

We will send your samples (without your name) to HVTN and HPTN approved labs for this study, which are located in the United States and South Africa. The samples will be tested to:

- measure how much antibody is in your blood,
- see how your immune system responds to the study products, and
- see if there is antiretroviral medicine (also called ART/ARV) in your blood.

Researchers may also do limited genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The differences in people's genes can help explain why some people get a disease while others do not. Limited genetic testing involves only some of your genes, not all of your genes (your genome). The researchers will only study the genes related to the immune system and HIV.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

In rare cases, some of your samples may be sent to HVTN and HPTN approved labs in other countries for research related to this study.

Tests done on your samples are for research purposes only. The labs will not give the results to you or this clinic, and the results will not become part of your study record.

Site: Delete next section if using separate consent for use of samples and information in other studies

14. When we take samples from you for this study, we take extra samples in case we have to repeat tests. When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these "extra samples."

This section gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

Do I have to agree? No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

Where are the samples stored? Extra samples are stored in a secure central place called a repository. [Site: choose one of the following two sentences. African sites should choose the sentence referencing the repository in South Africa. All other sites should choose the sentence referencing the repository in the United States]. Your samples will be stored in the HVTN repository in South Africa. Your samples will be stored in the HVTN repository in the United States.

How long will the samples be stored? There is no limit on how long your extra samples will be stored. [Site: insert limits if your regulatory authority imposes them.]

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

Will I benefit from allowing my samples to be used in other studies? Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

How do other researchers get my samples and information? When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: insert review by your institution's IRB/EC/RE, if applicable.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

What information is shared with other researchers? The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV prevention, the immune system, and other diseases.

Researchers may also do limited genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the

genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

15. We will counsel you on reducing your risk for HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior and drug use. We will provide you with condoms and lubricant. We will talk with you about ways of lowering your risk of getting HIV. We will help you develop a risk reduction plan. Some topics we may discuss include:

- What you think causes risky behavior for you
- Methods to avoid getting HIV or giving it to someone else

[Site: adjust the language in this paragraph about PrEP provision to meet local availability.] These methods may include not having sex, using condoms, or other behavior changes, such as cutting down on alcohol. We will talk about new methods of HIV prevention, including pre-exposure prophylaxis (PrEP), and help you evaluate if these methods are right for you. This study cannot directly provide or pay for PrEP, but if you are interested, we can give you information on how to access it.

[Site: The text in this paragraph applies to US sites only. Non-US sites adjust the language in this paragraph to meet local PrEP availability.] The HVTN, the HPTN, the Division of AIDS, and Gilead Sciences, Inc. (the maker of Truvada) have reached an agreement to provide Truvada as PrEP to study participants in HVTN 703/HPTN 081. If you are interested, clinic staff can give you more information about this program and can refer you to providers who can prescribe PrEP.

In this study, we will look at how many participants use PrEP. We will also try to find out if using PrEP has any effect on how VRC01 works.

16. If you are found to be HIV infected when you enroll, we will help you get care and support.

We will test your blood that we take during your first IV visit for HIV. It will take a few days to complete the tests. It might turn out that you were already infected with HIV before you got the antibody or placebo. If you were already infected with HIV before your first IV, you cannot stay in the study for its whole length. If that happens, we will tell you as soon as possible.

We will also ask you to come to the clinic for 3 more visits. At these visits, we will:

- Ask questions about your health;
- Perform physical exams based on your complaints or side effects;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on how to reduce your risk and ways to avoid transmission;
- Collect blood samples (about 35 mL or about 2 tablespoons each time); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

17. If you get infected with HIV during the study, we will help you get care and support.

If you become infected with HIV, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). We will ask you to come in for 3 additional visits over 6 months. You will not get any more IVs.

After your time in this study ends, we may invite you to join another study to follow your health and to see how your body controls your HIV infection. There will be a new consent form for this separate study that we will review with you.

18. We will do our best to protect your private information.

US sites: Check HIPAA authorization for conflicts with this section.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health, people who work for them, its study monitors, and its chosen South African representatives,
- The US Food and Drug Administration,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN and HPTN and people who work for them,
- The US National Institutes for Allergic and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.).

- [Item 1]
- [Item 2]
- [Item 3]

US sites: Include the following boxed text. You can remove the box.

We have a Certificate of Confidentiality from the US government, to help protect your privacy. With the certificate, we do not have to release information about you to someone who is not connected to the study, such as the courts or police. Sometimes we can't use the certificate. Since the US government funds this research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

Sites: The text below may not be deleted or changed, per FDA requirement. It's OK to remove the box around it.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At

most, the website will include a summary of the results. You can search this website at any time.

19. We may stop your IVs or take you out of the study at any time. We may do this even if you want to stay in the study and even if you were scheduled for more IVs.

This may happen if:

- you are unable to follow instructions,
- the researcher thinks that staying in the study might harm you,
- you enroll in a different research study where you receive another study product, or
- the study is stopped for any reason.

If we stop your IVs, we may ask you to stay in the study to complete other study procedures.

20. We will stop your IVs if you become pregnant during the study.

We will encourage you to stay in the study if you choose. We will discuss your study options with you. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

Other Risks

21. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of taking blood:

Taking blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of the IV procedures:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in infections.

Personal problems/discrimination:

Some people who join HVTN or HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry, get upset or angry, or assume that you are infected with HIV or at high risk and treat you

unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

HIV testing

HIV antibody tests are the usual way to test for HIV infections. Although 2 out of 3 people in this study will get an HIV antibody, we do not expect them to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the VRC01 antibody and none of them detected the antibody.

Although it has not been seen so far, getting VRC01 may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

To be absolutely safe we ask you to get HIV tests only at this clinic during the study. Our tests can always detect true HIV infection. They can also tell if someone is really not HIV infected. Since the antibodies do not last long in the body, we do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you are infected with HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

Risks of genetic testing:

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

U.S. Sites, include the following paragraph In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the antibody will increase, decrease, or not change your risk of becoming infected with HIV if exposed.

If we find that you were already HIV infected when you got the antibody, we do not know how the antibody will affect your HIV disease. We also do not know how having gotten it will affect your HIV-related lab results.

If you get infected with HIV during the study, we do not know how the antibody might affect the course of your HIV disease.

We do not know if getting this study product will affect how you respond to any future approved HIV prevention approach. It could be that a future HIV prevention approach may not work as well for you because you got the VRC01 antibody.

If you become pregnant while you still have VRC01 in your body, we don't know if it could be passed to your baby. We do not know how the antibody will affect a pregnant participant or a developing baby.

Benefits

22. The study may not benefit you.

Since we do not know if the antibody can prevent HIV infection in people, you should not expect any benefit from getting the antibody in this study. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

This study may show us that the VRC01 antibody can prevent HIV and the study results may also help in the search for methods to prevent HIV. However, if the VRC01 antibody later becomes approved and sold or leads to an HIV prevention method, there are no plans to share any money with you.

Your rights and responsibilities

23. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

24. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Injuries

Sites: Do not make changes to the following section without obtaining approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org.

25. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, there is a process to decide if it is related to the study product and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met. The funds may come from different groups, as described below.

Next paragraph for African sites except Zimbabwe.

(Sites: adjust the language in this paragraph so it is applicable to your site. Note: Insurance is purchased for all African countries except Zimbabwe. The ABPI guidelines may only apply to South Africa and Mozambique.) In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury. The insurance will follow the Association of the British Pharmaceutical Industry guidelines for payment of study-related injury. We can give you a copy of these guidelines. In rare cases, the insurance funds may not be enough. If needed, the HVTN and HPTN have limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Next paragraph for all other sites.

The HVTN and HPTN have limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Remaining paragraphs for all sites.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

26. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies.

27. In Section 14 of this form, we told you about possible other uses of your extra samples and limited information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your choice about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include limited genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing limited genetic testing, growing more of my cells, or genome wide studies.

28. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.

- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix B Approved birth control methods for African women (for sample informed consent form)

You should not become pregnant during the study because we do not know how the study antibody could affect the developing baby.

If you were born female and are sexually active in a way that could lead you to get pregnant, you must agree to use effective birth control from 3 weeks before your first IV until your last scheduled clinic visit (about 1¾ years after your first IV). You should not become pregnant during the study because we do not know how the antibody could affect the developing baby.

Effective birth control means using any of the following methods every time you have sex:

- Male or female condoms; or,
- Diaphragm or cervical cap;

PLUS 1 of the following methods:

- Birth control drugs that prevent pregnancy—given by pills, patches, vaginal rings, or inserts under the skin;
- Intrauterine device (IUD); or
- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.).

You do not have to use birth control if:

- You have reached menopause, with no menstrual periods for one year;
- You have had a hysterectomy (your uterus removed);
- You have had your ovaries removed;
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes; or
- You are sexually abstinent (no sex at all).

Appendix C Approved birth control methods for transgender men in the Americas (for sample informed consent form)

If you were assigned female at birth and are sexually active in a way that could lead to pregnancy, you must agree to use effective birth control from 3 weeks before your first IV until your last scheduled clinic visit (about 1¾ years after your first IV). You should not become pregnant during the study because we do not know how the antibody could affect the developing baby.

Although taking testosterone can lower the chances of becoming pregnant, it is not considered an effective method of birth control. Effective birth control means using any of the following methods every time you have sex:

- Drugs that are prescribed specifically for birth control and intended to prevent pregnancy—these include pills, shots, patches, vaginal rings, or inserts under the skin;
- Male or female condoms, with or without a cream or gel that kills sperm;
- Diaphragm or cervical cap with a cream or gel that kills sperm;
- Intrauterine device (IUD); or
- Any other contraceptive method approved by the researchers.

You do not have to use birth control if:

- You have had a hysterectomy (your uterus removed);
- You have had your ovaries removed;
- You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes; or
- You are sexually abstinent (no sex at all).

Appendix D Sample consent form for use of samples and information in other studies

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection

HVTN protocol number: HVTN 703/HPTN 081, The AMP Study

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. *[Site: choose one of the following two sentences. African sites should choose the sentence referencing the repository in South Africa. All other sites should choose the sentence referencing the repository in the United States].* Your samples will be stored in the HVTN repository in South Africa. Your samples will be stored in the HVTN repository in the United States.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

4. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: insert review by your institution's IRB/EC/RE, if applicable.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

8. What information is shared with other researchers?

The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV prevention, the immune system, and other diseases.

Researchers may also do limited genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

U.S. Sites, include the following paragraph

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect

you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact [name and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact [name/title/phone of person on IRB or other appropriate organization].

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your choice about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include limited genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above and also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing limited genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)

Participant's signature or mark

Date

Time

Clinic staff conducting consent
discussion (print)

Clinic staff signature

Date

Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)

Witness's signature

Date

Time

*Witness is impartial and was present for the consent process.

Appendix E Table of procedures (for sample informed consent form)

Procedure	Screening visit(s)	First IV visit	6 months 1 year 1½ years																						
			4 weeks	8 weeks	8 weeks + 5 days	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks	52 weeks	56 weeks	60 weeks	64 weeks	68 weeks	72 weeks	76 weeks	80 weeks	84 weeks	88 weeks
IV		√		√			√		√		√		√		√		√		√						
Medical history	√																								
Complete physical exam	√																								√
Brief physical exam		√		√			√		√		√		√		√		√		√						
Urine test	√			√																			√		
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test	√	√		√			√		√		√		√		√		√		√		√		√		√
HIV test & pretest counseling	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Risk reduction counseling	√	√		√			√		√		√		√		√		√		√		√		√		√
Interview/Questionnaire	√	√		√			√		√		√		√		√		√		√		√				√

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants

					Visit: Day: Week:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	
					Screening visit ³	D0 W0	D28 W4	D56 W8	D61	D84 W12	D112 W16	D140 W20	D168 W24	D196 W28	D224 W32	D252 W36	D280 W40	D308 W44	D336 W48	D364 W52	D392 W56	D420 W60	D448 W64	D476 W68	D504 W72	D532 W76	D560 W80	D588 W84	D616 W88	D644 W92		
						Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10							
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ⁴	Tube size (vol. capacity) ⁴																												Total
BLOOD COLLECTION																																
Screening/Diagnostic																																
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics ⁷	UW-VSL/ HSML-NICD	UW-VSL/ HSML-NICD	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20	260
Safety labs																																
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	55
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	55
STI Serology																																
Syphilis ¹¹	Local lab	Local lab	SST	5mL	—	5 ¹³	—	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	—	5 ¹³	—	—	—	—	—	20
Drug Levels/Detection																																
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0	
ARV detection ¹⁰	CSR	JHU	SST	8.5mL	—	y	—	y	—	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	0
Immunogenicity & Virologic Assays																																
Host genetics ⁵	CSR	FHCRC	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Anti-VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	y	—	—	—	—	—	—	—	—	—	—	—	y	—	—	—	0
Functional humoral assays ⁸	CSR	Duke/ SAIL-NICD	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0
Viral isolation/sequencing ⁹	CSR	TBD	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	250
STORAGE																																
Serum storage	CSR	—	SST	8.5mL	—	76.5	51	51	42.5	51	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	1139
PBMC storage	CSR	—	ACD	8.5mL	—	51	—	—	—	—	—	—	—	—	—	—	34	—	—	—	—	—	—	—	—	34	—	—	—	—	34	153
Visit total					15	163	71	81	63	71	73	63	78	63	73	71	107	63	78	63	73	63	73	63	112	71	63	63	63	107	1937	
56-Day total					15	178	249	330	215	286	287	206	213	203	213	206	250	240	247	203	213	198	208	198	247	245	245	196	188	232		
URINE COLLECTION																																
Urinalysis	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—		
Pregnancy Test ⁶	Local lab	Local lab			X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	
RECTAL SWAB COLLECTION																																
Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	—	X ¹³	—	—	—	—	—	
CERVICAL/VAGINAL SWAB COLLECTION																																
Trichomonas vaginalis	Local lab	Local lab			—	X ¹⁴	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	

¹ CSR = central specimen repository² Endpoint laboratories at UW-VSL, FHCRC, Duke, NVITAL, HSML-NICD, SAIL-NICD, and JHU. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); FHCRC = Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke = Duke University Medical Center (Durham, North Carolina, USA); NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa); SAIL-NICD = South African Immunology Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.⁴ Local labs may assign appropriate alternative tube types for locally performed tests.⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.⁶ Pregnancy test may be performed on blood specimens. Persons who are NOT capable of becoming pregnant due to having undergone a total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.10), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.¹⁰ Testing plan for ARV detection to be determined.¹¹ Syphilis testing will be done by serology in all cohorts.¹² Chlamydia/Gonorrhea testing will be done with urine and rectal swabs in MSM and TG cohorts, and with urine in the sub-Saharan Africa cohort of women.¹³ Syphilis and Chlamydia/Gonorrhea testing will be performed at visits 2, 9, 15 and 21 in MSM and TG cohorts. In the sub-Saharan Africa cohort of women, these tests will be performed at visit 2; thereafter, testing will only occur if indicated by symptoms.¹⁴ Cervical/vaginal swabs will be collected for Trichomonas testing at visit 2 in the sub-Saharan cohort of women; thereafter, testing will only occur if indicated by symptoms.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

Appendix G Schedule 2—Laboratory procedures for HIV-infected participants

					Visit:	#.X ⁵	201	202	203	204	205	206	207	208	
					Days after diagnosis:	D0	D7	D14	D21	D35	D49	D77	D105	D161	
					Weeks after diagnosis:	W0	W1	W2	W3	W5	W7	W11	W15	W23	
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³											Total
BLOOD COLLECTION															
Screening or diagnostic assays															
HIV diagnostics	UW-VSL/HSML-NICD	UW-VSL/HSML-NICD	EDTA	10mL	10	—	—	—	—	—	—	—	—	—	10
HIV PCR viral load	UW-VSL/HSML-NICD	UW-VSL/HSML-NICD	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	80
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5	5	5	5	5	5	5	5	5	5	45
Safety lab															
Hemoglobin	Local Lab	Local Lab	EDTA	5mL	—	—	—	—	—	5	—	5	—	—	10
Drug levels															
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	76.5
Immunogenicity & Virologic Assays															
Functional humoral assays ⁶	CSR	Duke/SAIL-NICD	SST	8.5mL	17	17	17	17	17	17	17	17	17	17	153
Viral isolation/sequencing	CSR	TBD	EDTA	10mL	10	10	10	10	10	10	10	10	10	10	90
Storage															
Serum	CSR		SST	8.5mL	25.5	17	17	17	17	17	17	17	17	17	161.5
Plasma	CSR		EDTA	5mL	5	5	5	5	5	5	5	5	5	5	45
PBMC	CSR		ACD	8.5mL	34	—	—	—	—	—	34	—	—	34	102
Visit total					115	72.5	72.5	72.5	72.5	77.5	106.5	77.5	106.5	773	
56-Day total					115	188	260	333	405	483	329	262	184		
URINE COLLECTION															
Pregnancy Test ⁴	Local Lab	Local Lab			X	—	—	—	—	—	X	—	—	—	

¹ CSR = central specimen repository

² HVTN Laboratory Program includes laboratories at UW-VSL, Duke, NVITAL, HSML-NICD, and SAIL-NICD. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); Duke-Duke = Duke University Medical Center (Durham, North Carolina, USA); NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa); SAIL-NICD = South African Immunology, Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ Pregnancy test may be performed on blood specimens.

⁵ Confirmatory draw for HIV diagnostics will be collected at this visit.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV infected at enrollment

					Visit:	#.X	201	202	Total
					Days after diagnosis:	D1	D14	D168	
					Weeks after diagnosis:	W0	W2	W24	
Procedure	Ship to ^{1,2}	Assay location ²	Tube Type ³	Tube size (vol. capacity) ³					
BLOOD COLLECTION									
Screening or diagnostic assays									
HIV diagnostics	UW-VSL/HSML-NICD	UW-VSL/HSML-NICD	EDTA	10mL	10	—	—		10
HIV PCR viral load	UW-VSL/HSML-NICD	UW-VSL/HSML-NICD	EDTA	10mL	—	10	10		20
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5	5	5		15
Storage									
Serum	CSR		SST	8.5mL	17	17	17		51
Visit total					32	32	32		96
56-Day total					32	64	32		
URINE COLLECTION									
Pregnancy Test ⁴	Local Lab	Local Lab			X	—	—		

¹ CSR = central specimen repository

² HVTN Laboratory Program includes laboratories at UW-VSL and HSML-NICD. UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ Pregnancy test may be performed on blood specimens.

Appendix I Schedule 1—Procedures at CRS for HIV-uninfected participants

Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Post
Day:	Screening	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D588	D616	D644	
Week:	visit ¹	W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	
Procedure	Scr.	Inf#1	Inf#2			Inf#3	Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9	Inf#10									
Study procedures²																											
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Risk reduction counseling	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Pregnancy prevention assessment ³	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Participant Questionnaire	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Concomitant medications	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Intercurrent illness/adverse experience	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
HIV infection assessment ⁴	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Local lab assessment																											
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine dipstick	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—	—
Pregnancy (urine or serum HCG) ⁵	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
CBC, differential	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
ALT, Creatinine	X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Syphilis ⁶	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—
Chlamydia, Gonorrhea ⁸	—	X ⁸	—	—	—	—	—	—	X ⁸	—	—	—	—	—	X ⁸	—	—	—	—	—	X ⁸	—	—	—	—	—	—
Trichomonas vaginalis (cervical/vaginal swab)	—	X ⁹	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Study product administration procedures																											
IV infusion ¹⁰	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Reactogenicity assessment ¹¹	—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Poststudy																											
Unblind participant	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

² For specimen collection requirements, see Appendix F.

³ Pregnancy prevention assessments are required only for participants who are capable of becoming pregnant.

⁴ Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

⁵ For a participant capable of becoming pregnant, pregnancy test must be performed on the day of infusion prior to infusion. Pregnancy test to determine eligibility may be performed at screening, but must also be done on Day 0 prior to infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.

⁶ Syphilis testing will be done by serology in all cohorts.

⁷ Syphilis and Chlamydia/Gonorrhea testing will be performed at visits 2, 9 15, and 21 in MSM and TG cohorts. In the sub-Saharan Africa cohort of women, these tests will be performed at Visit 2; thereafter, testing will only occur if indicated by symptoms.

⁸ Chlamydia/Gonorrhea testing will be done with urine with urine and rectal swabs in MSM and TG cohorts, and with urine in the sub-Saharan Africa cohort of women.

⁹ Cervical/vaginal swabs will be collected for Trichomonas testing at visit 2 in the sub-Saharan Africa cohort of women; thereafter, testing will only occur if indicated by symptoms.

¹⁰ Blood draws required at infusion visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests must be drawn within the 3 days prior to infusion.

¹¹ Reactogenicity assessments performed for 3 days postinfusion (see Section 7.8).

Appendix J Schedule 2—Procedures at HVTN CRS for HIV-infected participants

Visit Number:	#.X ^a	201	202	203	204	205	206	207	208
Days after diagnosis	D0	D7	D14	D21	D35	D49	D77	D105	D161
Weeks after diagnosis:	0	1	2	3	5	7	11	15	23
Study procedures^b									
Counseling on HIV-1 testing/diagnosis	X	X	—	—	—	—	—	—	—
Abbreviated physical exam	X	X	X	X	X	X	X	X	—
Complete physical exam ^c	—	—	—	—	—	—	—	—	X
ART assessment	X	X	X	X	X	X	X	X	X
Concomitant medications	—	X	X	X	X	X	X	X	X
Intercurrent illness/adverse experience	—	X	X	X	X	X	X	X	X
Transmission risk reduction counseling	X	X	X	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	—	—	—	—	—	—	—	X
Social impact assessment	X	X	X	X	X	X	X	X	X
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	X

^a Visit #.X = interim visit for the purpose of drawing samples for confirmatory HIV testing

^b For specimen collection requirements, see Appendix G.

^c Includes assessment of HIV/AIDS-related conditions.

Appendix K Schedule 3—Procedures at HVTN CRS for participants discovered to have been HIV infected at enrollment

Visit Number:	#.X ^a	201	206
Days after diagnosis	D0	D14	D168
Weeks after diagnosis:	0	2	24
Study procedures^b			
Counseling on HIV-1 testing/diagnosis	X	X	—
Abbreviated physical exam ^c	X	X	—
Complete physical exam	—	—	X
ART assessment	X	X	X
Concomitant medications	—	X	X
Intercurrent illness/adverse experience	—	X	X
Transmission risk reduction counseling	X	X	X
Behavioral risk assessment questionnaire	—	—	X
Social impact assessment	X	X	X
Social impact assessment questionnaire	—	—	X

^a Visit #.X = interim visit for the purpose of drawing samples for confirmatory HIV testing

^b For specimen collection requirements, see Appendix H.

^c Includes assessment of HIV/AIDS-related conditions.



PROTOCOL

HVTN 703/HPTN 081

**A phase 2b study to evaluate the safety and efficacy of
VRC01 broadly neutralizing monoclonal antibody in
reducing acquisition of HIV-1 infection in women in sub-
Saharan Africa**

DAIDS DOCUMENT ID 12045

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS
Bethesda, Maryland, USA

December 14, 2017
HVTN 703/HPTN 081
Version 4.0

Contents

1	Overview.....	5
1.1	Protocol Team	8
2	Background.....	11
2.1	Rationale for trial concept.....	11
2.2	bnAbs to HIV-1	12
2.3	VRC01: VRC-HIVMAB060-00-AB.....	15
2.4	Trial design rationale.....	16
2.5	Combination prevention for HIV acquisition.....	22
2.6	Plans for future product development and testing.....	25
2.7	Preclinical safety studies	26
2.8	Nonhuman primate (NHP) studies of VRC01.....	29
2.9	Clinical trial experience	32
2.10	Potential risks of study products and administration	40
3	Objectives and endpoints	42
3.1	Primary objectives and endpoints	42
3.2	Secondary objectives and endpoints	42
3.3	Exploratory objectives.....	43
4	Statistical considerations.....	44
4.1	Outline of the statistical considerations section	44
4.2	PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests	44
4.3	Statistical rationale for the 3-arm design compared to a 2-arm design	45
4.4	Sample size calculations for testing for overall PE (Primary objective 2)....	46
4.5	Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group.....	54
4.6	Sample size calculations for safety	55
4.7	Monitoring of the trial	56
4.8	Assessment of PrEP use	61
4.9	Randomization	61
4.10	Blinding.....	62
4.11	Statistical analyses.....	62
5	Selection and withdrawal of participants.....	77
5.1	Inclusion criteria.....	77
5.2	Exclusion criteria.....	79
5.3	Participant departure from infusion schedule or withdrawal	80
6	Study product preparation and administration.....	83
6.1	Study product regimen	83
6.2	Study product formulation	83
6.3	Preparation of study products.....	85
6.4	Administration.....	87
6.5	Acquisition of study products	88
6.6	Pharmacy records	88
6.7	Final disposition of study products	88

7	Clinical procedures	89
7.1	Informed consent	89
7.2	Pre-enrollment procedures	91
7.3	Enrollment and infusion visits	92
7.4	Post-infusion visits for HIV-uninfected study participants	94
7.5	HIV counseling and testing	95
7.6	Follow-up visits for HIV-infected participants	96
7.7	Follow-up visits for participants who discontinue infusions for reasons other than HIV infection	97
7.8	Contraception status	98
7.9	Urine testing	98
7.10	Assessments of reactogenicity	99
7.11	Visit windows and missed visits	100
7.12	Early termination visit	100
7.13	Pregnancy	100
8	HIV infection assessment and clinical response	101
8.1	HIV symptom assessment	101
8.2	HIV screening test (prior to randomization)	101
8.3	HIV testing postinfusion	101
8.4	Endpoint adjudication	102
8.5	HIV infection during the study	102
8.6	Medical care for participants who become HIV infected	103
9	Laboratory	104
9.1	CRS laboratory procedures	104
9.2	Total blood volume	104
9.3	Assay timepoints	104
9.4	VRC01 mAb levels	104
9.5	Endpoint assays: humoral	105
9.6	ARV detection	105
9.7	Host (human) genotyping	106
9.8	Lab assay algorithm	106
9.9	Possible additional studies	106
9.10	Other use of stored specimens	106
9.11	Biohazard containment	107
10	Safety monitoring and safety review	108
10.1	Safety monitoring and oversight	108
10.2	Safety reporting	109
10.3	Safety pause and prompt PSRT AE review	112
10.4	Review of cumulative safety data	113
10.5	Study termination	114
10.6	Social impact reporting	114
11	Protocol conduct	116
11.1	Emergency communication with study participants	117
12	Ethical considerations	118
13	IRB/EC/RE review considerations	120

13.1	Minimized risks to participants	120
13.2	Reasonable risk/benefit balance	121
13.3	Equitable subject selection	121
13.4	Appropriate informed consent.....	121
13.5	Adequate safety monitoring	122
13.6	Protect privacy/confidentiality	122
14	Version history.....	123
15	Document references (other than literature citations).....	129
16	Acronyms and abbreviations.....	131
17	Literature cited	134
Appendix A	Sample informed consent form	148
Appendix B	Approved birth control methods (for sample informed consent form)	168
Appendix C	Sample consent form for use of samples and information in other studies.....	169
Appendix D	Tables of procedures (for sample informed consent form)	174
Appendix E	Sample consent form for participants with HIV infection at enrollment or during the study	177
Appendix F	Schedule 1—Laboratory procedures for HIV-uninfected participants	181
Appendix G	Schedule 2—Laboratory procedures for HIV-1–infected participants	183
Appendix H	Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected	185
Appendix I	Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection	187
Appendix J	Schedule 1—Procedures at CRS for HIV-uninfected participants	188
Appendix K	Schedule 2—Procedures at CRS for HIV-1–infected participants	190
Appendix L	Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected	191
Appendix M	Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection.....	192
Appendix N	Protocol Signature Page	193

1 Overview

Title

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

Primary objectives

- To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in sub-Saharan African women
- To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in sub-Saharan African women

Study products and routes of administration

- VRC01:** human monoclonal antibody (mAb) VRC-HIVMAB060-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered at a final volume of 150 mL intravenously (IV)
- Control for VRC01:** Sodium Chloride for Injection 0.9%, USP administered at a volume of 150 mL IV

Table 1-1 Schema

			Infusion schedule (Weeks) [A = VRC01 infusion; C = Control infusion]											
	Treatment	N*	W0	W8	W16	W24	W32	W40	W48	W56	W64	W72	W80*	W104†
Group 1	VRC01 10 mg/kg	634*	A	A	A	A	A	A	A	A	A	A		
Group 2	VRC01 30 mg/kg	634*	A	A	A	A	A	A	A	A	A	A		
Group 3	Control	634*	C	C	C	C	C	C	C	C	C	C		
Total:			1900 (63300 VRC01 30 mg/kg; 633 VRC01 10 mg/kg; 634 control)											

* Due to the randomization scheme, the numbers of vaccine and control recipients may differ slightly.

♦ Week 80 is the last study visit for the primary endpoint analysis of prevention efficacy.

† Week 104 is the last study visit for the co-primary endpoint analysis of safety and tolerability.

Participants

1900 women in sub-Saharan Africa aged 18-40 who are at risk of HIV-1 infection; 2:1 active:control allocation; total approximately 1268 VRC01 mAb, 634 control

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

24 months of scheduled clinic visits

Estimated total study duration

60 months (includes enrollment and follow-up, including follow-up for HIV-infected participants)

Study product providers

Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

HIV Vaccine Trials Network (HVTN) Leadership Group/Core Operations Center, Fred Hutchinson Cancer Research Center (FHCRC) (Seattle, Washington, USA)

HIV Prevention Trials Network (HPTN) Leadership and Operations Center (LOC), FHI360 (Durham, North Carolina, USA)

Statistical and data management center (SDMC)

Statistical Center for HIV/AIDS Research and Prevention (SCHARP), FHCRC (Seattle, Washington, USA)

DF/Net Research (Seattle, Washington, USA)

Endpoint assay laboratories

- University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA);
- Duke University Medical Center (Durham, North Carolina, USA)
- FHCRC/University of Washington (Seattle, Washington, USA)
- South Africa Immunology Laboratory, National Institute for Communicable Diseases (SAIL-NICD) (Johannesburg, South Africa)
- HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (HSML-NICD) (Johannesburg, South Africa)

- NIAID Vaccine Immune T-Cell Antibody Laboratory (NVITAL) (Gaithersburg, Maryland, USA)
- (NIAID) Vaccine Research Center (VRC) (Bethesda, Maryland, USA)
- HPTN Laboratory Center, Johns Hopkins University (JHU) (Baltimore, Maryland, USA)
- University of Cape Town (UCT) (Cape Town, South Africa)
- University of Colorado, Denver (UC Denver) (Denver, Colorado, USA)

Study sites

Clinical Research Sites (CRSs) to be specified in the Site Announcement Memo

Safety monitoring

HVTN 703/HPTN 081 Protocol Safety Review Team (PSRT); NIAID Data and Safety Monitoring Board (DSMB)

1.1 Protocol Team

Protocol leadership

<i>Chair</i>	Lawrence Corey HVTN, FHCRC 206-667-6770 lcorey@fhcrc.org	<i>Statisticians</i>	Allan DeCamp SCHARP, FHCRC 206-667-7892 adecamp@scharp.org
<i>Chair</i>	Myron Cohen HPTN, University of North Carolina 919-966-2536 mscohen@med.unc.edu		Peter Gilbert SCHARP, FHCRC 206-667-7299 pgilbert@scharp.org
<i>Cochairs</i>	Srilatha Edupuganti Emory University 404-712-1434 sedupug@emory.edu		Michal Juraska SCHARP, FHCRC 206-667-5568 mjuraska@scharp.org
	Nyaradzo Mgodli UZ-UCSF Collaborative Research Programme, Harare, Zimbabwe 263-4-704890 nmmgodli@uz-ucsf.co.zw		Deborah Donnell SCHARP, FHCRC 206-667-5661 deborah@scharp.org
<i>Protocol Team leader</i>	Shelly Karuna HVTN Core, FHCRC 206-667-4355 skaruna@hvtn.org	<i>Medical officers</i>	Margarita Gomez Lorenzo Vaccine Research Program (VRP), DAIDS, NIAID 240-627-3510 gomezmm@niaid.nih.gov
<i>HVTN Laboratory lead</i>	John Hural HVTN Laboratory Program 206-667-1683 jhural@hvtn.org		David Burns Prevention Sciences Program (PSP), DAIDS, NIAID 301-435-8896 burnsda@niaid.nih.gov

Other contributors to the original protocol

<i>HVTN Core medical monitor</i>	Shelly Karuna HVTN Core, FHCRC	<i>DAIDS Protocol pharmacist</i>	Katherine Shin DAIDS, NIAID 240-627-3047
<i>Bioethics consultant</i>	Mark Barnes HPTN Ethics Working Group	<i>HVTN Regional medical liaison, Southern Africa</i>	Simba Takuva HVTN Core, FHCRC
<i>HVTN/HPTN Consultative investigators</i>	Ken Mayer Fenway Health, Boston, USA	<i>HVTN Regional clinical safety liaison for Africa</i>	Keitumetse Diphoko HCRISA
	LaRon Nelson Univ. of Rochester, Rochester, NY, USA	<i>HVTN Regional medical liaison, South America</i>	Robert De La Grecca HVTN Core, FHCRC
	Manuel Villarán IMPACTA, Lima, Peru	<i>HVTN Clinical safety specialist</i>	Maija Anderson HVTN Core, FHCRC
	Sinead Delany- Moretlwe Wits Reproductive Health and HIV Institute, Johannesburg, South Africa	<i>HVTN Statistical research associates</i>	Nidhi Kochar SCHARP, FHCRC

<i>Product developer representatives</i>	John Mascola VRC		Abby Isaacs SCHARP, FHCRC
	Barney Graham VRC		Jing Wang SCHARP, FHCRC
	Julie Ledgerwood VRC	<i>HVTN Social behavioral scientist</i>	Michele Andrasik HVTN Core, FHCRC
<i>HVTN Laboratory Program representatives</i>	On Ho HVTN Laboratory Program, FHCRC	<i>HPTN LOC director</i>	Nirupama Sista HPTN LOC, FHI360
	David Montefiori HVTN Laboratory Program, Duke Univ., Durham, NC, USA.	<i>HPTN Clinical research managers</i>	Philip Andrew HPTN LOC, FHI360
	Robert Coombs University of Washington Virology Specialty Laboratory, Seattle, WA, USA		Elizabeth Greene HPTN LOC, FHI360
<i>HPTN Laboratory Center representatives</i>	Susan Eshleman HPTN Laboratory Center (LC), Johns Hopkins Univ., Baltimore, MD, USA	<i>HVTN Clinical trials manager</i>	Carissa Karg HVTN Core, FHCRC
	Vanessa Cummings HPTN LC, Johns Hopkins Univ.	<i>HPTN SDMC Associate director</i>	Lynda Emel SCHARP, FHCRC
	Estelle Piwowar-Manning HPTN LC, Johns Hopkins Univ.	<i>HVTN SDMC Program manager</i>	Gina Escamilla SCHARP, FHCRC
<i>HVTN Regulatory affairs</i>	Megan Brandon HVTN Core, FHCRC	<i>HVTN Protocol development manager</i>	Carter Bentley HVTN Core, FHCRC
<i>Clinic coordinators</i>	Debora Dunbar University of Pennsylvania, Philadelphia, PA, USA	<i>HVTN Communications unit representative</i>	Jim Maynard HVTN Core, FHCRC

	Ana Patricia Rimachi Quiroz Asociación Civil Selva Amazónica, Iquitos, Peru	<i>HVTN Community engagement unit representative</i>	Gail Broder HVTN Core, FHCRC
	Christie Heiberg Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa	<i>HPTN Community program associates</i>	Jonathan Lucas HPTN LOC, FHI360
<i>Community Advisory Board (CAB) members</i>	Mark Hubbard Vanderbilt University, Nashville, TN, USA		Jontraye Davis HPTN LOC, FHI360
	Likhapha Faku HVTN Global CAB Member at Large, Rustenberg, South Africa	<i>Community educator/recruiters</i>	DaShawn Usher New York Blood Center, New York, NY, USA
	Jim Wick Bridge HIV. San Francisco, CA, USA		Luciana Kamel Instituto de Pesquisa Clinica Evandro Chagas (IPEC)
		<i>HVTN Technical editor</i>	Erik Schwab HVTN Core, FHCRC

2 Background

2.1 Rationale for trial concept

Effective biomedical interventions are needed to reduce the acquisition of HIV. The global HIV-1 epidemic continues and while many countries have made progress toward leveling HIV prevalence over the last few years, micro-epidemics of infection continue to occur in nearly all regions, even in countries possessing the full toolkit of proven prevention approaches [1-4]. The World Health Organization (WHO) estimates that there were 2 million new HIV infections worldwide in 2014, the last year for which data are available [5].

Antiretroviral drugs (ARVs) have been shown to be effective for HIV prevention in serodiscordant couples when administered to HIV-infected individuals as treatment as prevention (TasP) and clinical trials are now underway to evaluate the efficacy of TasP at a population level [6]. ARVs have also been shown to be effective as pre- or post-exposure prophylaxis (PrEP or PEP) [7]. At present daily oral emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) (Truvada) is the only drug approved for PrEP use, but this drug combination has significant known side effects [8]. The requirement for daily use and the side effect profile have made adherence to this drug regimen challenging, especially over long periods of time [9]. As a consequence, the capacity of currently available ARV regimens to reduce HIV incidence or prevalence is less than optimal. Furthermore, sustained use of ARVs for HIV prevention will increase the already significant burden of ARV manufacturing and delivery for HIV treatment, especially in countries bearing the highest burden of HIV disease. For these reasons, a biomedical HIV prevention approach that exhibits sustained activity over an extended time period, that has a safety profile acceptable for healthy persons, and whose effectiveness is less dependent upon individual adherence, is still needed.

An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies, a strategy that has been employed for more than 100 years against diverse disease targets and that is still used for hepatitis A and B prophylaxis [10,11] and for PEP for rabies, measles, varicella zoster, and other infectious diseases [12]. Most notably, palivizumab has been used for respiratory syncytial virus (RSV) prophylaxis in pre-term and other high-risk infants for nearly two decades. In 1998, a multinational, randomized controlled trial showed that palivizumab administered during the RSV season reduced RSV-associated hospitalizations by 39–78% in premature infants and in children with bronchopulmonary dysplasia [13]. Subsequent studies have confirmed palivizumab's safety, efficacy, and clinical benefit for infants at high risk for RSV infection [14,15]. Hence, palivizumab serves as a model for the use of mAbs to block a mucosally-acquired infection. Significantly, passive administration of this antibody has also set a standard by which candidate RSV vaccines are evaluated, by defining antibody levels that effectively inhibit fusion by RSV. This precedent has informed the conceptual framework for this study.

Over the past several years, there has been a concerted and notably successful effort to isolate broadly neutralizing antibodies (bnAb) to HIV-1 from chronically infected donors [16-32]. Subsequent research has provided considerable insight into the sites these antibodies target on HIV-1 and their functionality (ie, the mechanisms by which they neutralize the virus) [19,20,29,33]. This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies [34-37], prompting optimism that vaccines that elicit bnAbs against HIV-1 can be developed [35,38]. In addition, the availability of bnAbs against HIV opens the exciting possibility of antibody-mediated prevention (AMP) of HIV infection.

The Vaccine Research Center (VRC), NIAID, NIH has developed VRC01, a broadly neutralizing human mAb that targets the HIV-1 CD4 binding site [18]. This mAb was originally discovered in a participant infected with HIV-1 for more than 15 years who maintained viral control without use of antiretroviral therapy (ART) [39]. VRC01 has the capacity to neutralize a broad range of HIV-1 strains in vitro (Section 2.3) and has conferred protection against simian-human immunodeficiency virus (SHIV) challenges in nonhuman primate (NHP) studies [40-49] (Section 2.8). It has an acceptable safety profile, as seen in previous phase 1 studies (Section 2.9).

In addition to potentially developing a new HIV prevention modality, evaluating the preventive efficacy of mAbs can be expected to inform future HIV vaccine development. An important requisite for designing vaccines that elicit bnAbs is determining the level of neutralizing activity required to achieve a reasonable degree of protection in humans. It will also be important to know whether such levels vary by route of infection or neutralizing sensitivity of the infecting isolate. Notably, VRC01 contains the Fc portion of IgG1 and has demonstrated other effector functions. Evaluating the role of antibody-mediated effector functions (eg, antibody-dependent cellular cytotoxicity [ADCC], antibody-dependent cellular phagocytosis [ADCP], antibody-dependent cell-mediated viral inhibition [ADCVI], antibody-mediated virion capture in mucus, or inhibition of viral translocation across epithelial barriers, etc.) in protection is also of critical importance (see, eg, [50-53]).

Although it is not anticipated that this trial will lead directly to licensure, further assessment of this VRC01 product will depend on the results of this and other studies.

2.2 bnAbs to HIV-1

The last several years have seen a marked increase in the number of well-characterized bnAbs to HIV-1. [Figure 2-1](#) shows the names and binding sites of many of these.

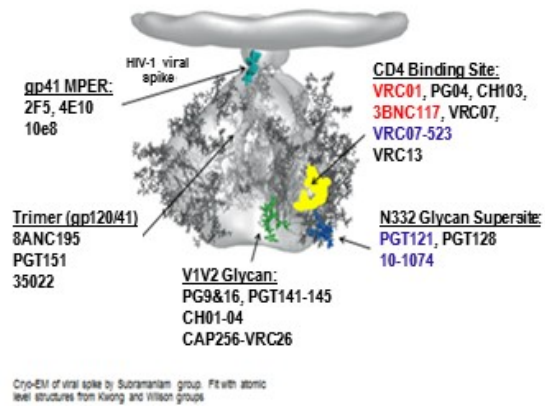


Figure 2-1 Neutralizing antibody epitopes on native Env trimer

As shown in [Figure 2-2](#), several of these antibodies have shown considerable breadth of neutralization in in vitro testing.

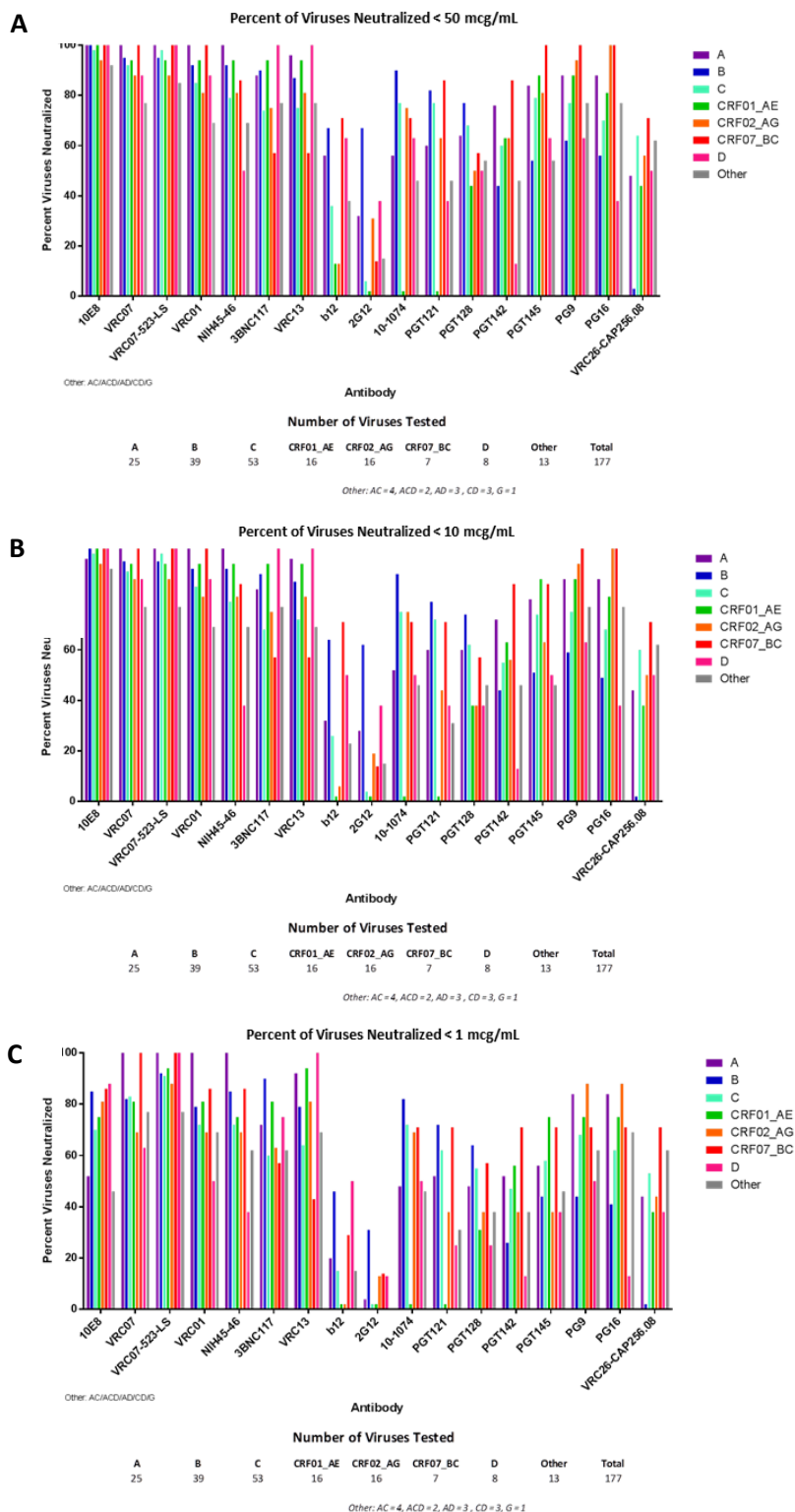


Figure 2-2 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL [32,49,54-57].

Two antibodies to the CD4 binding site of the HIV-1 envelope, VRC01 and 3BNC117 (highlighted in red in [Figure 2-1](#)), have entered phase 1 clinical trials.

2.3 VRC01: VRC-HIVMAB060-00-AB

VRC01 is a human mAb, developed by VRC/NIAID/NIH, directed against the CD4-binding site of HIV-1. The bulk lot of the drug substance was manufactured under current Good Manufacturing Practice (cGMP) conditions in a Chinese Hamster Ovary (CHO) cell line and the drug product vials were filled and labeled at the VRC Vaccine Pilot Plant (Frederick, Maryland, USA) operated by Leidos Biomedical Research, Inc. (formerly SAIC-Frederick), Frederick, Maryland (USA). Product is vialled at a concentration of 100 mg/mL VRC01 in formulation buffer containing 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. VRC01 was produced using recombinant DNA technology. Briefly, using polymerase chain reaction (PCR) amplification and cloning of the heavy and light chain variable region genes, a mAb was initially isolated from a single B cell from an HIV-1–infected subject who displayed bnAbs. VRC01 is an IgG1 antibody and is highly somatically mutated from the germ-line precursor.

The VRC01 antibody has been well characterized preclinically and has demonstrated favorable characteristics in potency and half-life [19]. In addition, it has demonstrated protection in NHP challenge studies (see Section 2.8.1 below). [Figure 2-2](#) shows graphically the impressive breadth of VRC01, with 90% of 190 HIV-1 isolates across all clades tested showing sensitivity to neutralization by VRC01. As shown in [Figure 2-3](#), VRC01 has a 50% inhibitory concentration (IC_{50}) of < 50 mcg/mL against 91% of primary HIV-1 isolates and IC_{50} < 1 mcg/mL against 72% of HIV-1 isolates. Notably, the IC_{50} for the vast majority of HIV-1 isolates tested is < 1 mcg/mL; the geometric mean IC_{50} for HIV-1 strains from all clades tested is 0.33 mcg/mL.

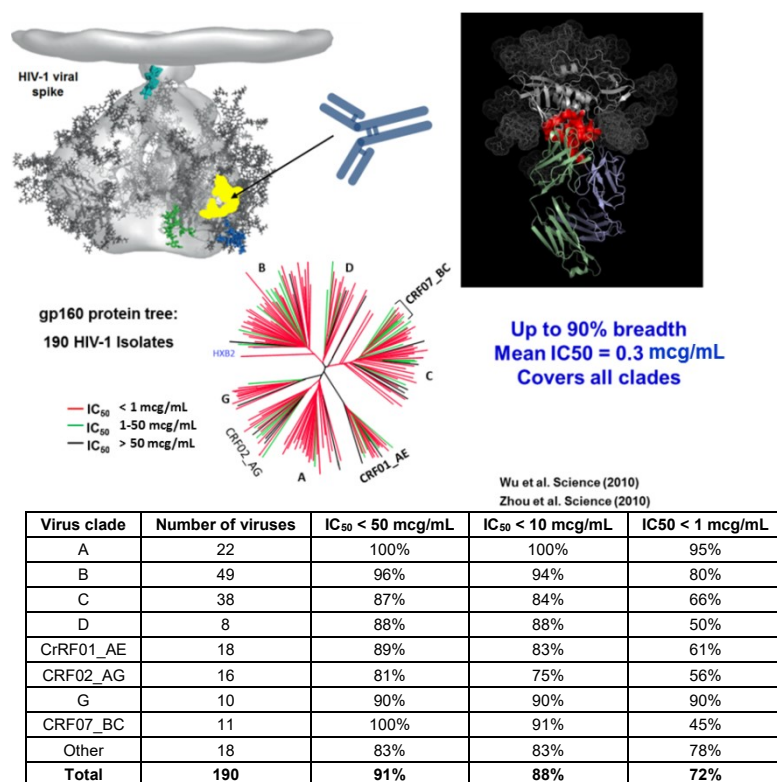


Figure 2-3 CD4 binding site antibody: VRC01 [18,19]

Details on VRC01 composition and manufacturing can be found in the investigator's brochure (IB).

2.4 Trial design rationale

Several considerations inform the design of this test-of-concept phase 2b study. The first is to establish that passive administration of bnAbs can block HIV acquisition. Based on data from in vitro neutralization studies, the NHP challenge studies described below, and pharmacokinetic (PK) data from the phase 1 clinical trials VRC 602 and HVTN 104, the doses selected are designed to elucidate the activity of the antibody across a range of serum concentrations in a diverse population of at-risk persons in multiple geographic regions of the world. The study is designed to define the optimal dosage for widespread use of the antibody or its subsequent derivatives as well as to benchmark the types of effector functions associated with efficacy, thus constituting an important bridge to other types of bnAbs and other bnAb delivery systems.

Inclusion of different doses (ie, in a 3-arm study) is important for a number of reasons. First, while the in vitro and NHP challenge data are informative, the VRC01 antibody serum level required to provide protection against HIV-1 infection in humans is unknown. Some studies suggest that transmitted-founder HIV strains may be more sensitive to neutralization than other strains (particularly by VRC01) [58,59], and therefore potentially susceptible to even lower antibody

doses than those suggested by SHIV challenge studies in NHP. It must also be recognized that the lowest challenge doses used in the NHP model likely exceed natural exposure in the majority of transmissions in humans.

Defining the lowest efficacious VRC01 dose is essential for establishing a target product profile (TPP), including optimal dosing for clinical use, for this antibody and its derivatives. Typically, higher doses of drug products are associated with lower tolerability due to side effect profiles or operational features such as length of drug administration time (eg, IV infusion time). At present the high dose (30 mg/kg) cannot be administered subcutaneously (SC), limiting the feasibility of long-term clinical use. The extreme difficulty of scaling IV administration to the populations most in need of protection against HIV infection and the complexity and cost of manufacturing mAbs would severely limit implementation of this potentially important HIV prevention tool if higher doses are required for efficacy. Therefore, it is important to evaluate the efficacy achieved at lower antibody concentrations. That lower doses of mAbs may prevent HIV acquisition is supported by the high percentage of isolates susceptible in vitro to antibody concentrations as low as 1 mcg/mL of VRC01, 1/10 the mean trough level anticipated with 30 mg/kg VRC01 dosing every 8 weeks.

Including a range of doses in this study also facilitates evaluation of antibody effector functions, in addition to neutralization, that are associated with protection (eg, virion binding, ADCC, ADCP). Note that the relationship of these important functions to neutralization is not linear and therefore cannot be inferred directly. This information will have important implications for the development of other bnAbs and other biomedical HIV prevention modalities.

Hence, in addition to providing a test of concept for AMP for HIV, if breakthrough infections are observed, the data generated by this trial will help guide development of functionally-enhanced mAbs and of long-term delivery strategies (eg, vaccine immunogen or vectored immunoprophylaxis). This trial affords a unique opportunity to correlate serum antibody levels and the potency of effector functions with protective efficacy in a trial in which these parameters can be measured close to the time of HIV acquisition, providing benchmarks for vaccine development and helping define “targets” of antibody effector mechanisms for protein or viral vector based vaccines. The data will also provide critical information by which to identify which NHP models (eg, SHIV challenge stocks) are most predictive of bnAb efficacy in humans.

2.4.1 Cohort selection

The study will be conducted in 1900 sexually active women in sub-Saharan Africa. The trial sample size is designed to provide 90% power to detect a prevention efficacy (PE) of 60% (rejecting the null hypothesis of 0% PE), based on reasonable assumptions regarding background HIV-1 incidence, retention, and frequency of infusions.

The cohort for this study was selected based on regional epidemiological data. There were approximately 24.7 million people living with HIV in sub-Saharan Africa in 2013, representing over 70% of the global HIV burden. HIV prevalence in sub-Saharan Africa continues to be higher than anywhere else in the world. Women in sub-Saharan Africa are disproportionately impacted, accounting for nearly 60% of all people living with HIV in the region in 2013. There are approximately 16 million women ≥ 15 years old who are living with HIV; 80% live in sub-Saharan Africa. Young women 15-24 years old in sub-Saharan Africa are twice as likely as young men to be living with HIV, with acquisition rates among heterosexual women as high as 6-8% annually in some locations [60]. In recent clinical trials in southern Africa, annual HIV-1 incidence rates of 1.9-9.1% have been observed among sexually-active women [61-67]. Yet, there are currently no biomedical HIV prevention tools proven to protect women at high risk of HIV infection in sub-Saharan Africa. Fortunately there are biomedical tools with demonstrated HIV prevention success for men at high risk of HIV infection in sub-Saharan Africa (eg, medical male circumcision, oral PrEP). With this context in mind, and recognizing that we have limited resources for this trial that prevent us from addressing the HIV prevention needs of all populations, this trial in sub-Saharan Africa is designed to: evaluate the effectiveness of AMP, inform future research on AMP and related prevention approaches (eg, HIV vaccines), and develop a biomedical tool to reduce the disproportionate HIV incidence among sub-Saharan African women. Conducting the study in heterogeneous cohorts of overall lesser risk (eg, men as well as women in sub-Saharan Africa), would require larger sample sizes in order to answer the study questions. We look forward to extending what we learn in this trial to other cohorts, including men at high risk of HIV infection in sub-Saharan Africa.

We note that a parallel study assessing the safety and preventive efficacy of VRC01 is being conducted among 2700 men and transgender persons who have sex with men or transgender persons in the Americas and Europe. That study, designated HVTN 704/HPTN 085, will be conducted over approximately the same time period as HVTN 703/HPTN 081.

2.4.2 Dose and schedule

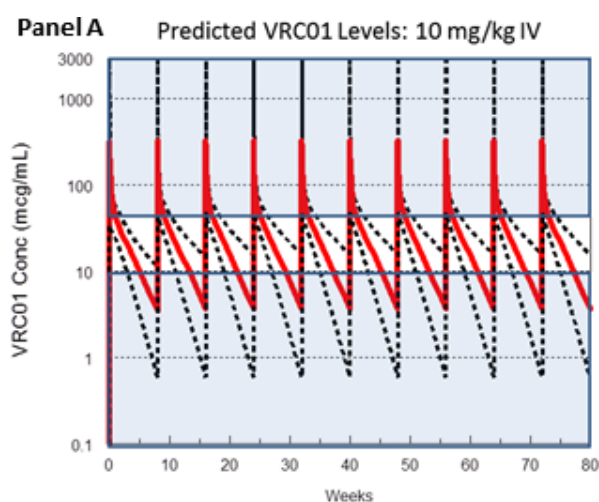
An equal number of study participants will be randomized to receive VRC01 mAb by IV infusion at a dose of 10 mg/kg or 30 mg/kg every 8 weeks, or to receive control infusions every 8 weeks. The 8 week infusion interval represents approximately 4 half-lives of the study drug (half-life ~ 14 days based on previous clinical testing; see the IB).

Infusions will continue for 72 weeks for all groups, with a final primary follow-up visit (without infusion) at week 80 and an additional 24 weeks of follow-up without infusions. Hence, the study duration for each participant is 104 weeks (2 years).

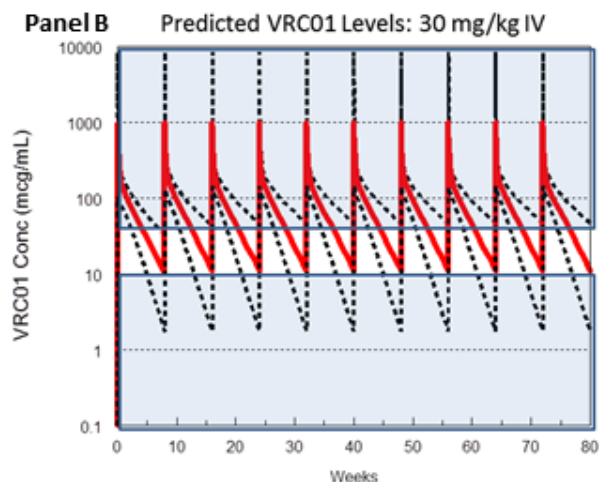
Projected serum concentrations of VRC01 are shown in [Figure 2-4](#). This figure plots predicted median VRC01 serum concentrations over time based on PK

models for VRC01 administered at 10 mg/kg every 8 weeks (Panel A) and for VRC01 administered at 30 mg/kg every 8 weeks (Panel B). The plots include shaded regions illustrating time regions where the study participants have serum concentrations in low, medium, and high ranges. Based on in vitro neutralization studies (see Section 2.3) and NHP challenge studies (see Section 2.8.1) and assuming that these accurately predict protection in humans, the expected trough levels of VRC01 are projected to be an order of magnitude higher than the levels required to protect against a majority of circulating HIV-1 strains.

See Section 2.9.3 and Figure 2-9 for VRC01 serum concentrations reported to date for participants administered 10mg/kg and 30mg/kg of VRC01 every 8 weeks in HVTN 104.



10 mg/kg VRC01 group: Predict (50%, 40%, 10%) PYRs in (Low, Medium, High) zones



30 mg/kg VRC01 group: Predict (10%, 40%, 50%) PYRs in (Low, Medium, High) zones

Figure 2-4 Predicted VRC01 serum concentrations over time. Panel A: Predicted VRC01 median serum concentration over time (solid lines) for 10 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72, with 95% confidence intervals (CI) (dashed lines). The shaded regions classify the serum concentration marker $S(t)$ into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. Panel B: Predicted median VRC01

serum concentration over time for 30 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72. The shaded regions classify the serum concentration marker S(t) into high, medium, and low ranges based on the cut-points 10 and 50 mcg/mL. PYR = person-year at risk.

There is a substantial overlap in the mAb concentrations between the low and high dose groups during a considerable period of time after each infusion. This is shown in [Figure 2-5](#).

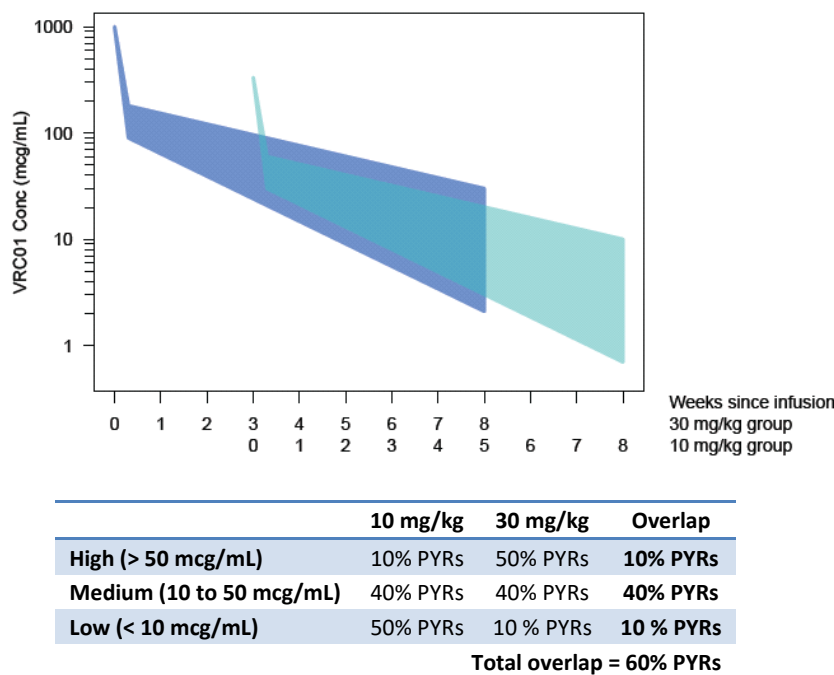


Figure 2-5 Projected overlap in serum VRC01 concentrations and PYRs of HIV exposure between high dose (30 mg/kg) and low dose (10 mg/kg) VRC01 administration

2.4.3 Choice of control

Sodium Chloride for Injection 0.9%, USP (referred to as Control) administered IV at a volume of 150 mL will serve as an inert control.

Use of a placebo control in this trial is warranted based on the scientific and public health importance of the questions it seeks to answer, the necessity of a placebo control in order to assess VRC01 efficacy in preventing HIV-1 infection, and an acceptable risk/benefit ratio considering the minimal risk associated with the placebo control selected and its administration via a procedure commonly used in clinical care. In addition, the placebo control is essential to maintain double-blinding to ensure unbiased assessments of study product safety and efficacy, and the use of the placebo control is disclosed fully to study participants (see Section 10 of [Appendix A](#)). Hence, this trial meets the standards commonly required for ethical use of placebo controls in clinical trials [68-70].

2.4.4 HIV diagnostic testing

HIV diagnostic testing will be scheduled at least every four weeks and at any time following participant report of possible exposure during the study. See Section 8 for further detail on HIV-infection assessment. Participants who are diagnosed with HIV infection after enrollment will not receive additional infusions. Infusions will also be permanently discontinued for participants who have 2 reactive HIV tests, even if subsequent testing indicated that the participant is not HIV infected. Based on the schedule of testing, it is possible that a newly infected participant may receive an infusion of VRC01 (or Control). This does not appear to pose a safety risk for participants based on existing preclinical, clinical, and in vitro data. Specifically, passively-infused VRC01 given to NHP on Day 7 after SHIV SF162P3 infection reduces viremia and does not cause clinical harm (see IB). Additionally, passive transfer of neutralizing antibodies (at non-protective levels) prior to infection improved control of SHIV viremia and was associated with early nAb development in infected infant macaques [71]. Furthermore, VRC01 has been evaluated in viremic and aviremic HIV-infected participants (see Section 2.9.1). VRC01 administration is associated with statistically significant transient reductions in HIV viral load in adults with chronic HIV infection (see IB), and HIV variants that escape from in vitro VRC01 neutralization have reduced viral fitness [72]. Studies evaluating VRC01 in acutely infected subjects are being initiated based on these data.

2.4.5 Trial monitoring

As this is the first large-scale phase 2b study with IV administration of a biomedical intervention for prevention of sexual HIV-1 transmission, the trial design includes an early feasibility check. After approximately 120 participants have completed the Week 32 visit, a treatment-blinded analysis of infusion feasibility will be conducted and reported to the DSMB. Enrollment of the remaining study participants will be deemed feasible if $\geq 80\%$ of those 120 participants remain engaged in the trial and have not declined further infusions. Enrollment will not be paused for this feasibility assessment.

In addition to the feasibility assessment, the study design includes sequential monitoring for potential harm, non-efficacy, high efficacy, and futility for assessing prevention efficacy. Following similar monitoring procedures developed and implemented for the HVTN 505 phase 2b vaccine efficacy trial, potential harm monitoring is maximally vigilant by testing for a higher HIV infection rate among VRC01 recipients than in the control group after each HIV infection and providing the results to the DSMB after each infection starting with the 20th total infection pooled over the study groups. This ensures that any potential risk of increased HIV acquisition (negative prevention efficacy [PE]) would be detected as early as possible, such that infusions of the mAb could be discontinued expeditiously. In addition, the operating characteristics of the trial (Figure 4-3 and Table 4-2) show that this potential harm-monitoring approach has a low risk of stopping the study prematurely if the true PE is 0% or higher. The

non-efficacy monitoring is conducted approximately every 6 months, and is based on a trigger specified in the study monitoring plan.

At the 6-month intervals, statistical interim analysis reports are provided to the DSMB. Gilbert et al [73] describe the conceptual approach to the sequential monitoring of PE, where the implementation for the current trial is slightly different. Additional information is provided in Section 4.7. Full details regarding implementation of monitoring for this trial are contained in a separate trial monitoring plan.

2.5 Combination prevention for HIV acquisition

In 2013, sub-Saharan Africa bore more than 70% of the global burden of HIV infections and women accounted for nearly 60% of all those living with HIV in the region. Of all the women in the world who live with HIV, 80% live in sub-Saharan Africa [60]. Hence it is essential that approaches to reducing HIV infection risk be made available to the women participating in this clinical trial.

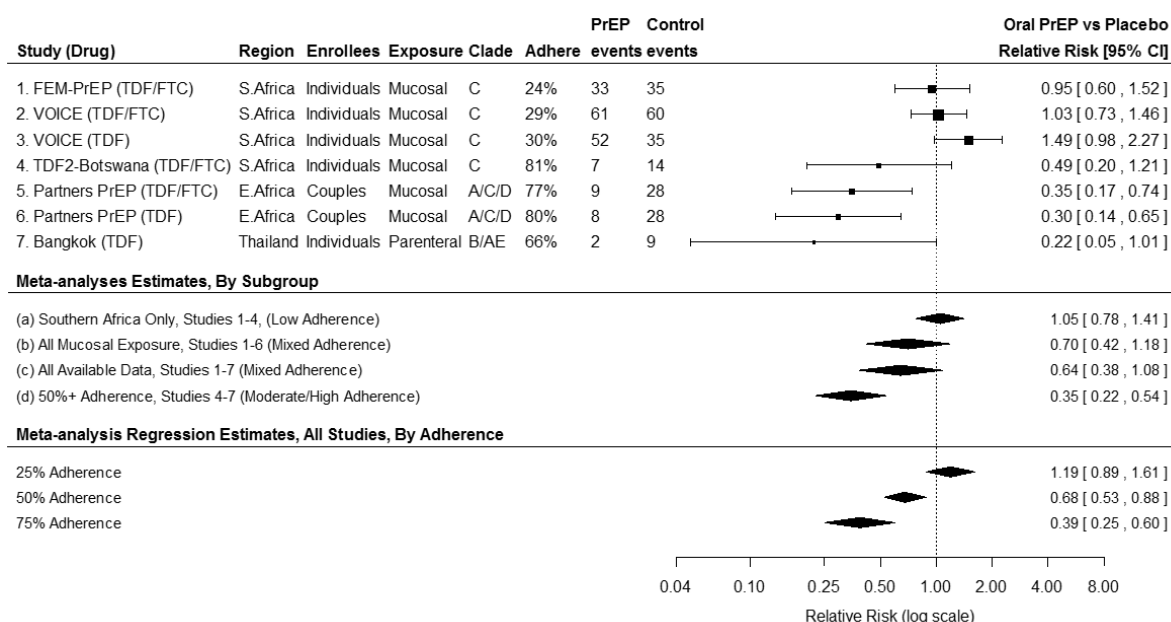
Participants in all arms of the study will be provided with a comprehensive HIV prevention package consistent with all HIV prevention clinical trials. This package includes evidence-based behavioral risk reduction counseling [74], free condoms and lubricant, counseling and referral for postexposure prophylaxis (PEP) when indicated, and, where appropriate, access to oral drugs for pre-exposure prophylaxis (PrEP, see below). These activities can be expected to reduce HIV acquisition below historical levels. The contribution of these efforts will be monitored. Further details on these efforts are provided in the HVTN 703/HPTN 081 Study Specific Procedures (SSP) and the HVTN 703/HPTN 081 website. It should be emphasized that because the benefit of VRC01 monoclonal antibody is unknown, subjects in each arm of the study will receive the same prevention package.

2.5.1 Evidence for PrEP efficacy

Multiple studies in multiple settings have established that daily or pericoital FTC/TDF can be highly efficacious in preventing HIV infection in MSM [7,75-79]. However, aside from women in HIV-discordant couples [80], comparable efficacy has not as consistently been demonstrated in trials evaluating topical or oral tenofovir (TFV)-based regimens among at-risk women in sub-Saharan Africa. While the CAPRISA 004 trial demonstrated a 39% reduction in HIV infection with pericoital application of TFV 1% vaginal gel among at-risk women in South Africa [65], efficacy was not seen in the larger, more recent FACTS 001 trial conducted among young South African women [81]. In 2011 the FEM-PrEP trial was stopped early because of lack of efficacy of once daily oral FTC/TDF among at-risk women in Kenya, South Africa, and Tanzania [66]. In 2011 the VOICE trial, conducted in Uganda, South Africa, and Zimbabwe, reported no efficacy of once daily oral TDF or TFV 1% gel; in 2013, this trial reported no efficacy for once daily oral FTC/TDF [82]. A meta-analysis of these trial results

shows that effectiveness correlates strongly with PrEP adherence (see Figure 2-6)[83]; because adherence was poor in the trials that generated the largest number of infection events (FEM-PrEP and VOICE), overall PrEP efficacy in southern African trials appears particularly disappointing. However, in addition to adherence, other factors may also contribute to the conflicting results observed in women, including differences in the study populations (discordant couples versus uninfected individuals), differing demographic and behavioral characteristics, prevalent HIV subtypes, differing transmission modes (mucosal versus parenteral), and underlying host factors such as genital tract inflammation and/or copathogens [83]. In addition, pharmacokinetic studies report lower concentrations of PrEP drug in vaginal as compared to rectal mucosa [84], suggesting that efficacy mediators may differ between men and women and that PrEP efficacy may be more sensitive to adherence in women than in men [85].

Figure 2-6 Forest plot showing point estimates and 95% confidence intervals of PrEP effectiveness, meta-analysis estimates, and meta-analysis regression results for major PrEP trials in women [83]



2.5.2 Evolving PrEP guidelines

Guidelines for use of fixed dose FTC/TDF for HIV prophylaxis have evolved rapidly. In 2011, the US Centers for Disease Control and Prevention (CDC) issued interim guidelines for use of FTC/TDF as PrEP for high-risk MSM [86]. In 2012, the US FDA approved FTC/TDF for HIV prophylaxis in persons at high risk for HIV infection. That same year, the World Health Organization (WHO) issued guidance on the use of PrEP for serodiscordant couples and for men and TG women who have sex with men [87]. In 2014, the US CDC issued a further PrEP guidance document and a Clinical Provider Supplement confirming the previous recommendation of FTC/TDF PrEP as a prevention option for sexually-active adult MSM at substantial risk of HIV acquisition and expanding the

recommendation to include adult heterosexually active persons at substantial risk of HIV acquisition [88,89]. PrEP has since been incorporated into WHO guidelines for ARV use for HIV treatment and prevention [90,91]; a revised and more comprehensive WHO PrEP guideline is anticipated in 2016. Notably, the Republic of South Africa and Kenya approved FTC/TDF for use as PrEP in December 2015.

2.5.3 Operationalizing PrEP access in sub-Saharan Africa

Although the WHO released updated guidance documents on universal test and treat and recommendations for PrEP in late 2015, most countries in this region are in the process of regulating antiretrovirals for prevention, and it is envisaged that PrEP use will be scaled up over time in the ensuing 5-10 years. Going to scale in a generalized heterosexual epidemic will require significant financial investment. For this reason, countries are currently investigating the fiscal impacts of the new guidelines and are in discussions to develop demonstration projects to evaluate mechanisms for the successful roll out of PrEP to key populations. The threshold for PrEP roll-out in-country will depend on: 1) the epidemiology context; 2) availability of resources; 3) the cost of the intervention; 4) the feasibility of delivering this service; and 5) demand. There are limited donor-driven demonstration PrEP projects in Africa and countries are working closely with PEPFAR and the Global Fund to design demonstration projects that are potentially sustainable in the long-term.

As an example, South Africa recently registered FTC/TDF for prevention and is developing guidelines for its use. These guidelines stipulate that prep must be delivered in the service delivery setting with the main guiding principal of informed and voluntary choice and equitable access. There is a commitment by the Republic of South Africa to strategically expand the reach and coverage of the antiretroviral programme in such manner of it being equitable and non-discriminatory. Although FTC/TDF is not yet available in the public sector for use in prevention, the South African government through the National Department of Health (NDOH) intends to conduct demonstration projects, in conjunction with key donors, in key populations such as sex workers and MSM, as well as in geographic locations that have a high burden of HIV. However, FTC/TDF for prevention is not yet on the Essential Drug List, which is a prerequisite for use in the public sector through which the vast majority of South Africans secure health care.

Currently an investment case evaluating the new WHO guidelines is being undertaken by the South African government. While the investment case for universal test and treat is clear, and this will be rolled out as a priority, the investment case for PrEP is less certain and is being evaluated. Initially the NDOH plans to evaluate PrEP in key population groups such as sex workers and MSM. The roll-out of PrEP in young women is more complex and the NDOH is developing guidelines as to how this may occur.

For these reasons, the protocol team plans to work collaboratively with national regulatory and other government agencies to develop mechanisms for PrEP access that are supportive of and consistent with national priorities and strategic objectives in the several sub-Saharan African countries where this study is being implemented.

Given the potential of FTC/TDF to prevent HIV acquisition, it could be argued that substantial uptake of PrEP could prevent the HVTN 703/HPTN 081 trial from detecting any benefit of VRC01 beyond the universal prevention package. This possibility is addressed in the sample size and power calculations (see Section 4.4) and in plans for trial monitoring by the DSMB (see Section 4.7 and, specifically, Section 4.7.3). If the background HIV incidence rate is too low to support evaluation of VRC01 prevention efficacy, the DSMB will detect this and will make recommendations to the team accordingly. The study team will monitor PrEP availability and roll-out in-country; and within the protocol, evaluate individual use via questionnaires and blood drug levels. In support of a comprehensive package of prevention, PrEP will be discussed in the informed consent process, in risk reduction counseling sessions, and referral systems into demonstration projects, health service delivery settings, and the private sector will be developed to support those who wish to access PrEP.

2.6 Plans for future product development and testing

VRC01 is considered to have potential value for both preventive and therapeutic purposes across broad geographic regions of the HIV-1 epidemic. The product was initially evaluated in phase 1 studies to characterize PK and distribution in HIV-infected and HIV-uninfected adults (VRC 601 and 602, respectively; see Sections 2.9.1 and 2.9.2) and PK and safety for multiple administrations under several route and dosing regimens are being evaluated currently (HVTN 104; see Section 2.9.3). In parallel, IMPAACT P1112 will evaluate the safety of VRC01 in high-risk infants born to HIV-infected mothers; data from this study will support a future evaluation of the efficacy of VRC01 administered to high-risk infants shortly after birth and continued through the period of breast-feeding for prevention of mother-to-child HIV transmission (PMTCT).

The development of VRC01 for clinical use depends on a number of factors, the most critical of which is the level of efficacy demonstrated by the current study. If the antibody proves to be highly effective at preventing HIV-1 infection, its development will depend on identifying a partner able to provide large-scale manufacturing. Other factors that could influence advanced development of VRC01 or similar monoclonal antibodies include: 1) the potential for improving the potency of the product to allow use at a lower dose and perhaps by an SC route, 2) the potential for increasing the half-life of the product to allow less frequent dosing, and 3) the potential to use VRC01 or its derivatives in combination with other neutralizing mAbs to increase potency and breadth of coverage. Efforts to address these issues are proceeding in parallel with the

current study, but the outcome of the current study will have the greatest influence on the future clinical use of VRC01 in adult prevention or PMTCT.

2.7 Preclinical safety studies

2.7.1 Preclinical toxicology and PK study of VRC01 in rats

Table 2-1 Summary of preclinical studies

Study number	Product	Type of study	Animal	N	Dose groups	Route	Schedule
SRI No M896-11	VRC-HIVMAB060-00-AB	Repeat dose toxicity	Sprague-Dawley rats	10m, 10f each 50m, 50f total	Vehicle* 4mg/kg IV 40 mg/kg IV 400 mg/kg IV 40 mg/kg SC	IV & SC	D1, D8
SRI No M896-11	VRC-HIVMAB060-00-AB	Single-dose PK	Sprague-Dawley rats	9m, 9f each 27m, 27f total	4 mg/kg IV 40 mg/kg IV 40 mg/kg SC	IV & SC	D1

* Vehicle consists of VRC01 formulation buffer.

A repeat dose toxicity study of IV and SC administration and a single dose PK study was performed by SRI International (Menlo Park, CA) with VRC01 in male and female Sprague-Dawley rats in accordance with US FDA “Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies” (Table 2-1). This study was conducted with a pre-GMP pilot lot of VRC01 manufactured at smaller scale using a similar purification process to that of the GMP clinical grade drug product.

For the safety assessment, various doses of VRC01 (4 mg/kg, 40 mg/kg, or 400 mg/kg) or a comparable control vehicle was administered by tail vein infusion on Days 1 and 8 to Groups 1 through 4, respectively. An additional group (Group 5) received 40 mg/kg VRC01 via SC administration to the dorsal scapular region on Days 1 and 8. Each group contained 10 male and 10 female rats. Five animals of each sex were sacrificed on Day 9, one day after the second administration; the remaining animals were sacrificed on Day 30, 22 days after the second administration.

Results obtained showed that both routes of administration were well tolerated in the rats. All animals survived until their scheduled necropsy. No findings or changes were seen in clinical observation, body weight, food consumption, body temperature, infusion site irritation, hematology, coagulation, or organ weight evaluations that are attributed to administration of VRC01. VRC01 administration resulted in small, transient, dose-dependent increases in aspartate

aminotransferase (AST) and alkaline phosphatase (ALP) on Day 9. By Day 30, AST values had returned to normal, and ALP values were returning to normal.

Other than red discoloration of the administration site in one male in the SC group on Day 9, there were no other gross necropsy observations attributable to VRC01 administration. There were no histopathology findings that were considered related to IV administration of VRC01.

The pre-specified IV dose studied in rats was 400 mg/kg and SC was 40 mg/kg, which will greatly exceed the dose levels in the adult clinical studies. A “no observed effect level” (NOEL) was not determined in this study because transient elevations of AST and ALP were observed on Day 9 after IV administration and transient inflammation at the dose site was observed on Day 9 after SC administration. Because the elevated AST and ALP levels were transient and minor and did not correlate with histopathology findings, the no observed adverse effect level (NOAEL) for VRC01 by the IV route of administration in rats was 400 mg/kg, the highest dose used in this study.

For the PK analysis, 3 groups of rats (9 males and 9 females in each group) received VRC01 on Day 1 at 4 mg/kg IV, 40 mg/kg IV, and 40 mg/kg SC respectively. VRC01 levels in serum were determined using an enzyme-linked immunosorbent assay (ELISA) with samples collected predose from each animal and from an additional 3 males and 3 females to provide untreated control serum. Blood was collected from 3 rats/sex/PK group for a total of 4–5 collections per PK animal at each of the following postdose timepoints: 1, 4, 8, 24, 48, and 72 hours and 7, 14, 21, and 29 days.

VRC01 administration by the IV route resulted in dose-proportional exposure. The terminal elimination phase half-life was about 10 days, with clearance of approximately 20 mL/day/kg and volume of distribution that was about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. VRC01 administration by the SC route resulted in mean peak serum levels at 7 days for male or 3 days for female animals. The maximum serum concentration and area under the concentration-time curve to the last timepoint values were lower when 40 mg/kg was administered by the SC route compared with the IV route. The bioavailability of 40 mg/kg VRC01 administered by the SC route was estimated to be 31.4% (males) and 42.3% (females). After the peak concentration of VRC01 was achieved in the SC group, the serum levels decreased much more rapidly from 7 to 14 days than they did in the IV groups, and VRC01 concentrations in the SC group were not quantifiable at timepoints after 14 days. These data indicate that clearance of VRC01 in rats was markedly enhanced when it was administered by the SC route. The development of anti-drug antibodies that contribute to an increased rate of clearance is often observed in preclinical safety studies of protein-based test articles when they are not tested in the species of origin. Although immunogenicity was not examined in this study, the presence of such antibodies might have contributed to the increased rate of clearance of VRC01 after SC administration that was observed in this study [92,93].

2.7.2 Tissue cross reactivity GLP study of VRC01 with human tissues in vitro

A tissue cross-reactivity study of VRC01 using normal adult and neonatal human tissues in vitro (Testing Facility Study No. A255-12) was performed by Charles River Laboratories (Reno, NV) in accordance with U.S. FDA “Good Laboratory Practice for Nonclinical Laboratory Studies” (GLP). The tissue panels used as the test system for this *in vitro* cross-reactivity study included all of the tissues on the “Suggested list of human tissues to be used for immunohistochemical or cytochemical investigations of cross reactivity of monoclonal antibodies” in Annex I of the “European Medicines Agency Guideline on Development, Production, Characterization and Specifications for Monoclonal Antibodies and Related Product, Adopted by the Committee for Medicinal Products for Human Use on December 18, 2008” and all of the tissues recommended in the FDA/Center for Biologics Evaluation and Research “Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (February 28, 1997).” In addition, the tissue cross-reactivity study used additional neonate/infant tissues suggested by the FDA to support future trials in infants.

To determine the cross-reactivity of VRC01 binding, VRC01 was applied to cryosections from a full panel of tissues from normal human adults and a limited panel of human neonatal tissues, immunohistochemically detected using a biotinylated rabbit anti-human IgG secondary antibody, and binding was visualized with a streptavidin-horseradish peroxidase complex and a diaminobenzidine chromogen substrate. VRC01 binding was evaluated at concentrations of 5 and 50 mcg/mL.

Specific VRC01 staining was not observed in any normal adult human or neonatal human tissues evaluated. Therefore, in vitro evaluation of cross-reactivity in tissue specimens did not identify potential tissue sites or organ systems to more thoroughly evaluate in subsequent preclinical studies, and it supports the future use of VRC01 in humans.

2.7.3 Other toxicity studies

Several in vitro studies were conducted to assess antibody activity against self-antigens by VRC01. Several anti-HIV neutralizing mAbs will cross-react to lipid or nuclear antigens or Hep-2 cells [94,95]. Anti-lipid binding activity is understandable when considering that the HIV-1 gp41 protein is membrane-spanning and the epitopes (MPER: Membrane-Proximal External Region) recognized by some mAbs (eg, 4E10 and 2F5) are membrane-proximal and likely extend into the membrane itself. Therefore, the ability (or lack thereof) of VRC01 to cross-react with lipids was assessed in collaboration with Dr. Barton Haynes of Duke University. Binding of antibody to cardiolipin was assessed in a luminescent assay, expressed in relative units. VRC01 was compared to 4E10, an anti-gp41 mAb known to bind to cardiolipin and nuclear antigens, and Synagis, a licensed anti-RSV antibody used as a negative control. Synagis is included

because it is the licensed mAb product most analogous to the intended clinical use of the VRC mAb [13].

Individual studies are summarized in [Table 2-2](#). Unlike other anti-HIV neutralizing mAbs, VRC01 does not react to phospholipids or anti-nuclear antigens or Hep-2 cells. Additional details are provided in the IB.

Table 2-2 In vitro preclinical safety studies

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC01 does not react to phospholipids
Assessment of anti-nuclear antigen reactivity	VRC01 does not react with nuclear antigens
Assessment of anti-phospholipid characteristics by impact on activated partial thromboplastin time (aPTT)	VRC01 does not impact aPTT by binding phospholipids
Assessment of Binding to a Human Cell Line by Immunohistochemistry	Fluorescently labeled VRC01 does not bind Hep-2 cells

2.8 Nonhuman primate (NHP) studies of VRC01

Several non-Good Laboratory Practices (ie, non-GLP) studies of VRC01 have been completed in NHP to assess for preclinical evidence of potential efficacy for prevention of HIV infection. [Table 2-3](#) summarizes the studies performed.

Table 2-3 Summary of NHP pharmacology and challenge studies

Study	Product	Animal	N	Dose/Route	Infusion schedule	Challenge route	Challenge stock/dose	Challenge schedule
Pharmacology	VRC01 (Pilot lot)	Rhesus macaques	4f 4f	40 mg/kg IV 40 mg/kg SC	Day 0	NA	NA	NA
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4m 4m 4m	5 mg/kg IV 20 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-SF162P3 (300 TCID ₅₀ *)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	4f 4f	20 mg/kg IV Human IgG IV (control)	Day 0	Intravaginal	SHIV-SF162P3 (300 TCID ₅₀)	Day 2 postinfusion
High-dose challenge	VRC01 (Research Grade)	Rhesus macaques	6m 6m 4m 16m 14m	20 mg/kg IV 5 mg/kg IV 1.25 mg/kg IV 0.3 mg/kg IV Human IgG IV (control)	Day 0	Intrarectal	SHIV-BaL (TCID ₅₀ 12,800 in TZM-bl)	Day 2 postinfusion

*TCID₅₀ = 50% tissue culture infectious dose

In the pharmacology study, plasma and mucosal (ie, rectal, vaginal, and nasal) samples were collected at frequent intervals through Day 28. A dose of 40 mg/kg IV or SC in female rhesus macaques resulted in plasma concentration of VRC01

exceeding 50 mcg/mL in 7 of 8 animals at Day 14 and greater than 10 mcg/mL in 7 of 8 animals at Day 28.

Please see the VRC01 IB for more details.

2.8.1 Protection against challenge in NHP models

Both neutralizing and non-neutralizing antibodies to HIV and SIV have been shown to protect against experimental challenge in the NHP model [40-42,96-100]. In these studies the degree of protection has varied with the neutralizing potency of the antibodies and with the dose, route, and sensitivity of the challenge stocks. Low antibody concentrations have in some instances been quite protective, especially against repeat low-dose mucosal challenges [44,45]. However, neutralization-resistant SHIVs have been developed and have been shown to be resistant to protection [101,102]. This has permitted estimation of neutralization titers for different mAbs against SHIVs representing a broad range of neutralization resistance.

VRC01 has been tested in several NHP challenge experiments (see [Table 2-3](#)). In a rectal challenge model with SHIV BaLP4, a dose of 20 mg/kg IV protected 6/6 NHP; a 5 mg/kg IV dose protected 6/6; and a 0.3 mg/kg IV dose protected 2/6 [47]. Using a more resistant SHIV-162P3 challenge, a 20 mg/kg IV dose protected all 4 male animals from rectal challenge and all 4 female animals from vaginal challenge [47]. Analyses of the combined data from the NHP challenge studies show complete protection against SHIV162P3 challenge at a VRC01 plasma concentration of 50 mcg/mL and partial protection (IC_{50} [50% inhibitory concentration]) at 20 mcg/mL. For the more sensitive BaLP4 virus the IC_{50} is only 1.5 mcg/mL. Based on preclinical studies, an antibody serum concentration of about 40 to 50 mcg/mL is projected to provide protection against the vast majority of circulating strains of HIV [103]. In the NHP studies, both the virus sensitivity and serum antibody titers appear to influence protection from mucosal challenge. A summary of serum concentrations associated with protection against diverse SHIV strains of varying resistance to neutralization is shown in [Figure 2-7](#).

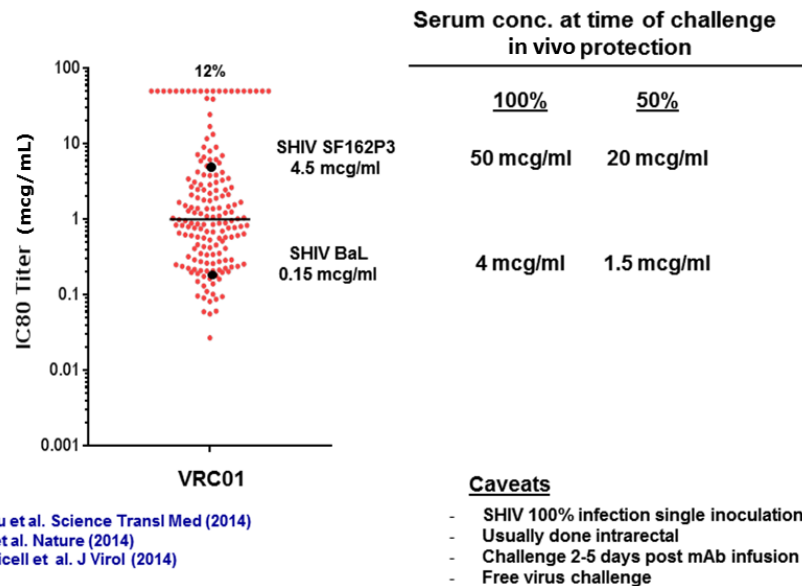


Figure 2-7 VRC01 IC₈₀ values (170 Isolates) and serum concentrations in NHP SHIV challenge studies

It is particularly interesting to note that following administration of VRC01 to NHP, the antibody is found in mucosal tissues (see [Figure 2-8](#)). This is likely a product of active antibody transport to mucosal tissues through neonatal Fc receptor (FcRn) binding [48].

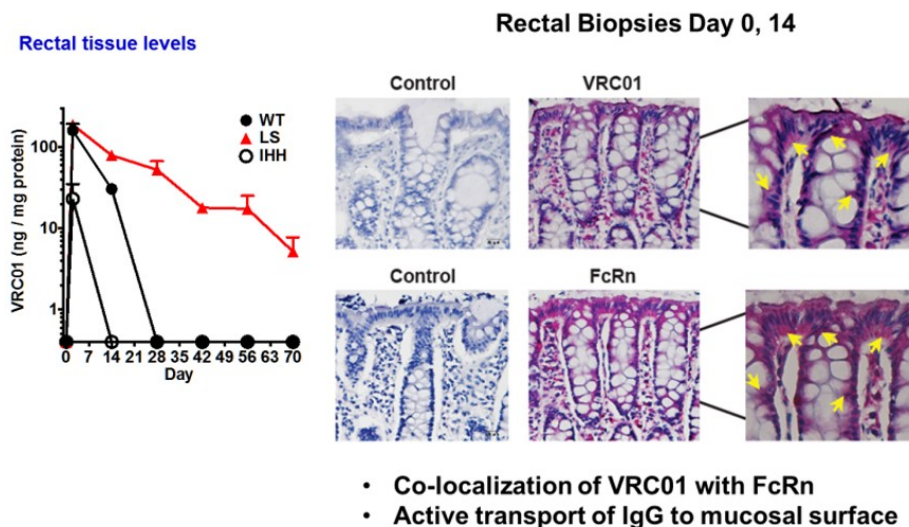


Figure 2-8 VRC01 mucosal pharmacokinetics in rhesus macaques [48]

NHP challenge studies have also shown that, in addition to classic neutralization, bnAbs such as VRC01 often elicit antibody-mediated cellular effector functions [45,104]. As a result, protection against experimental challenge has sometimes been achieved with notably low doses of VRC01 [47,103]. Similar mechanisms of protection have been implicated in studies of other bnAbs showing protection despite barely detectable neutralization activity (1:1) at challenge [44].

Recent NHP studies of VRC01 and other highly potent mAbs, such as PGT121, demonstrate protection at infusion doses of 5 mg/kg and even at 1 mg/kg [46,49,103,105]. There is also evidence that such protection can be durable; a simianized version of VRC01 was shown to protect monkeys against SHIV challenge nearly 8 weeks after their last 5 mg/kg antibody infusion, when plasma concentrations of VRC01 ranged from ~0.5 mcg/ml to undetectable [105]. These data suggest that a 10 mg/kg infusion dose of VRC01 administered every 8 weeks may offer protection against HIV acquisition.

Please see the VRC01 IB for more details on the NHP challenge studies.

2.9 Clinical trial experience

Completed phase 1 clinical studies of VRC01 include first-in-humans dose escalation studies for safety, tolerability, and PK assessments in HIV-infected (VRC 601) and HIV-uninfected (VRC 602) adults. Studies to characterize the neutralizing activity and other functional assays as a function of plasma concentration are also underway. As of April 2017, more than 1200 clinical trial participants have received VRC01 in phase 1 trials and in the phase 2b AMP studies.

Both the IV and SC routes of administration have been evaluated. Ultimately, the best route for clinical use may depend upon the age of the recipient (adult or infant), stage of product development, formulation, and important considerations related to volume needed and maintenance of a target VRC01 blood level considered to be in the therapeutic range.

2.9.1 VRC 601

VRC 601 (NCT01950325) titled, “*A Phase 1, Open-Label, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), with Broad HIV-1 Neutralizing Activity, Administered Intravenously or Subcutaneously to HIV-Infected Adults.*”

VRC 601 (Table 2-4) was the first study of the VRC01 mAb in HIV-infected participants [106]. It was a dose-escalation study to examine safety, tolerability, dose, PK, and anti-antibody immune responses. VRC 601 opened in September 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and in total, 23 HIV-infected participants, including 15 aviremic ARV-treated participants and 8 viremic non-ARV treated participants, were infused with one or two doses of VRC01 at doses up to 40 mg/kg IV.

Table 2-4 VRC 601 study schema

VRC 601 Dose Groups		VRC01 Administration Schedule	
Group	No. of evaluable participants*	Day 0	Week 4
1	3-5	1 mg/kg IV	1 mg/kg IV
2	3-5	5 mg/kg IV	5 mg/kg IV
3	3-5	5 mg/kg SC	5 mg/kg SC
4	3-5	20 mg/kg IV	20 mg/kg IV
5	3-5	40 mg/kg IV	40 mg/kg IV
Total	15-25	IV doses administered in 100 mL of normal saline over 30-60 minutes. SC doses administered in the minimum volume at 15 mL/hr. *Only participants who begin infusion are evaluable. Only 3 evaluable participants per group will be enrolled into the dose group until the safety review is completed. Additional slots are available, if needed, to have sufficient data for the safety review or to include at least one eligible subject with a detectable viral load later after the dose escalation is complete.	

The first infusion at 1 mg/kg IV was administered in the VRC 601 study on September 30, 2013. Beginning on March 28, 2014, the dose escalation proceeded according to the schema. The first 40 mg/kg IV administration in this study occurred May 12, 2014 and the last infusion in VRC 601 occurred on April 6, 2015. All IV and/or SC infusions have been well-tolerated with no serious adverse events (SAEs) or dose limiting toxicity.

VRC 601 demonstrated evidence of VRC01-mediated antiviral effect. An interim analysis of the VRC 601 viral load data obtained from 8 viremic adults through April 30, 2015 shows that VRC01 has a statistically significant in vivo virological effect on HIV viral load when administered as a single 40 mg/kg IV dose. None of these adults were taking antiretroviral therapy (ART) when enrolled into the study and had not started ART during the time period when the viral load data were collected. Six of the eight adult participants had $\geq 1 \log_{10}$ copies/mL decrease in viral load and two participants had a viral load drop of 0.26 and 0.18 $\log_{10}$ copies/mL respectively. These interim data indicate the following for a single dose of VRC01 at 40 mg/kg IV:

- A statistically significant change from baseline viral load postinfusion days 5 to 16;
- The median time to reach $\geq 0.5 \log_{10}$ decrease in viral load is 5 days; and,
- The median time to greatest decrease in viral load is 7 days.

A 0.5 $\log_{10}$ copies/mL or greater decrease in viral load is considered to be a positive response to ART. To have clinical benefit, such a change would need to be sustained. In VRC 601, participants were administered only one dose of

VRC01 at 40 mg/kg and, thus, a sustained effect on viral load was not expected. However, the data demonstrate a VRC01 mediated anti-viral effect.

2.9.2 VRC 602

VRC 602 (NCT01993706) is titled, “*A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB060-00-AB (VRC01), Administered Intravenously or Subcutaneously to Healthy Adults.*”

VRC 602 was the first study of the VRC01 mAb in HIV-uninfected adults. It was a dose-escalation study to examine safety, tolerability, dose, and PK of VRC01 [107]. VRC 602 opened in December 2013 as a single site study at the NIH Clinical Center, Bethesda, Maryland and the final infusion was administered in August 2014.

As shown in [Table 2-5](#), there were 3 open-label, dose escalation groups (Groups 1, 2, and 3) for IV administration and 1 double-blinded, placebo-controlled group (Group 4) for SC administration.

Table 2-5 VRC 602 study schema

VRC 602 Groups			VRC01 Administration Schedule	
Group	Initial Enrollments	Additional Enrollments	Day 0	Week 4
1	3	2	5 mg/kg IV	5 mg/kg IV
2	3	2	20 mg/kg IV	20 mg/kg IV
3	3	2	40 mg/kg IV	40 mg/kg IV
4	SC administration			
4A	3	2	5 mg/kg SC	5 mg/kg SC
4B	3	2	Placebo SC	Placebo SC
Total		25	20 participants treated with VRC01 at different dosage levels and 5 participants treated with placebo administered SC	
IV doses administered in 100 mL of normal saline over 1 hr. First SC dose administered at about 15 mL/hr via SC infusion pump; subject option for second dose administration (Week 4) by direct SC injection with needle and syringe.				

All IV and/or SC infusions were well-tolerated with no SAEs or dose limiting toxicity.

PK analysis from VRC 602 revealed a VRC01 terminal half-life of 15 days across all IV infused dose groups. After the first infusion, 28-day trough levels were 35 mcg/mL and 57 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively. Following the second infusion, the 28-day trough values rose to 57 mcg/mL and 89 mcg/mL for the 20 mg/kg and 40 mg/kg dose groups, respectively [107].

In addition, after infusion VRC01 retained the expected neutralizing activity in serum and no anti-VRC01 antibodies were detected [107].

2.9.3 HVTN 104

HVTN 104, titled *A phase I clinical trial to evaluate the safety and drug levels of a human monoclonal antibody, VRC-HIVMAB060-00-AB (VRC01) administered in multiple doses intravenously and subcutaneously in different dosing schedules to healthy, HIV-uninfected adults*, is examining safety profiles and serum levels of 5 different regimens for the IV and SC administration of VRC01 (Table 2-6). IV administration is being evaluated at doses of 10, 20, 30, and 40 mg/kg; SC administration is being tested at 5 mg/kg.

Table 2-6 HVTN 104 study schema

Dose Groups		Study product administration schedule in months (days)											
Group	N	0	0.5 (14)	1 (28)	1.5 (42)	2 (56)	2.5 (70)	3 (84)	3.5 (98)	4 (112)	4.5 (126)	5 (140)	5.5 (154)
1	20	VRC01 40mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV		VRC01 20mg/kg IV	
2	20	VRC01 40mg/kg IV				VRC01 40mg/kg IV				VRC01 40mg/kg IV			
3	20	VRC01 40mg/kg IV	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC	VRC01 5mg/kg SC
	4	IV placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01	SC placebo for VRC01
4	12	VRC01 10mg/kg IV				VRC01 10mg/kg IV				VRC01 10mg/kg IV			
5	12	VRC01 30mg/kg IV				VRC01 30mg/kg IV				VRC01 30mg/kg IV			
Total	88	Intravenous (IV) doses administered in 100 mL of normal saline over 1 hr Subcutaneous (SC) doses administered by needle and syringe injection											

HVTN 104 is a phase 1 clinical trial designed to evaluate the safety and drug levels of VRC01 administered in multiple intravenous or subcutaneous doses and different dosing schedules to 88 healthy, HIV-uninfected adults at 6 HVTN CRSs in 4 US cities: Boston, New York, Philadelphia, and Cleveland. The first participant enrolled in HVTN 104 on September 9, 2014 and the last participant enrolled on July 15, 2015. Study product administration for all participants was complete as of November 30, 2015. The study has 5 arms: Group 1 is evaluating the IV administration of a 40 mg/kg loading dose, with 2 subsequent 20 mg/kg doses given at 8 week intervals. Groups 2, 4, and 5 are evaluating 3 infusions of 40 mg/kg, 10 mg/kg, or 30 mg/kg, respectively, given 8 weeks apart. Group 3 is evaluating 5 mg/kg given every 2 weeks subcutaneously for 24 weeks after an initial IV administration at 40 mg/kg; this will inform the design of perinatal

prophylaxis studies. Secondary aims of HVTN 104 are: (1) to evaluate the kinetics of *in vitro* neutralization in serum of a single VRC01 sensitive virus isolate (TZM.bl assay); (2) to determine whether anti-idiotypic antibody (AIA) can be detected and whether there is a correlation of VRC01 levels and AIA levels in serum; (3) to determine if measurable levels of VRC01 can be found in genital, rectal, and oral secretions; (4) to evaluate the kinetics of *in vitro* neutralization in mucosal secretions of a single VRC01 sensitive virus isolate; and (5) to assess binding of VRC01 to multiple Env proteins.

A total of 249 IV infusions and 208 SC injections of VRC01 were administered in HVTN 104. The infusions and injections were well tolerated, with 28% of infusions and 14% of injections associated with mild pain and/or tenderness. 55% of VRC01 and 50% of placebo recipients experienced mild pain and/or tenderness at the infusion or injection site sometime during the trial. One participant experienced moderate pain and/or tenderness following a SC injection of VRC01. Mild infusion site erythema/induration reactions were reported for 2 VRC01 participants and 1 placebo recipient. Two moderate erythema/induration reactions were reported. 1 following IV VRC01 and 1 following VRC01 SC injection. For 76% of the infusions and injections administered in the trial, no systemic reactogenicity symptoms were reported. 56% of VRC01 and 75% of placebo recipients experienced systemic reactogenicity symptoms following at least one study product administration. These were all graded as mild in the placebo recipients; of VRC01 recipients who experienced any systemic symptoms, the maximum severity was mild in 70%, moderate in 23%, and severe in 6% (3 participants). The most commonly reported symptoms were malaise/fatigue, headaches, and myalgias.

The severe systemic reactogenicity symptoms reported in 3 VRC01 recipients are detailed as follows:

- 1 participant developed severe malaise, myalgia, headache and chills, mild nausea, and moderate arthralgia symptoms within 3 days after the first infusion of study product. These symptoms had resolved by Day 7. The participant had a concomitant AE of laboratory confirmed Influenza A infection diagnosed on Day 2 and was treated with Ibuprofen.
- 1 participant reported a viral illness AE of moderate intensity beginning 3 days prior to the 9th SC injection (10th study product administration), characterized by nausea and vomiting, sore throat, runny nose but no fevers; a household contact was also ill. At baseline on Day 0 of the 9th SC injection, mild malaise/fatigue was still present. At the early assessment timepoint on Day 0, this was still present and also grade 1 nausea. Within 3 days of the injection, the participant developed severe malaise, myalgia, headache, chills, and arthralgia; these all resolved on Day 6, which was the date the AE for viral illness was resolved. There was no reported use of concomitant medications for these symptoms.

- 1 participant reported severe malaise/fatigue on the day of the first infusion, resolving spontaneously the next day. During this reactogenicity period, this participant also reported a grade 1 headache on Day 1, resolving the next day.

There were no study product discontinuations due to reactogenicity symptoms.

There were 235 AEs occurring in 70 participants (79.5%), with similar rates of occurrence across all treatment groups. 74% of AEs were graded as mild, 22.5% as moderate, and 3.4% as severe. 9 AEs (3.8% of all AEs) occurring in 8 participants were deemed product-related by the investigators; all were mild and transient. Those occurring following VRC01 administration included elevations of hepatic transaminases (AST and ALT in 1 individual), elevated creatinine, neutropenia, localized injection site pruritus, diarrhea, generalized rash, and Varicella zoster infection. No VRC01-related hypersensitivity reactions or CRS symptoms were observed during the study.

Study product administration was discontinued in 8 participants. Reasons for discontinuing study product included: AEs (3 participants), relocation from study site (2), unable to adhere to visit schedule (1), unable to contact (1), and pregnancy (1). Of those participants for whom study product was discontinued due to an AE, 1 participant developed a mild, localized pruritic, maculopapular rash 3 days after receiving the first SC injection of VRC01, which resolved within 4 hours after applying inert lotion; this was deemed related to study product. Another participant had a brief syncopal episode several hours after receiving a VRC01 infusion; this was deemed not related to study product. A third participant had mild, brief chest tightness following the first SC injection that resolved spontaneously; this was deemed related to study product, however this participant was determined after unblinding to have received the placebo. In sum, VRC01 was well-tolerated when administered IV or SC.

Of note, safety experience with VRC01 has remained consistent whether 1-2 doses were administered, as in VRC 601 and 602, or multiple doses were administered, as in HVTN 104. No trends toward recurrence of lab abnormalities or AEs deemed related to study product or increase in frequency or severity of local or systemic reactogenicity symptoms has been observed with multiple administrations of VRC01.

Figure 2-9 shows serum VRC01 levels following the first 2 infusions (samples collected as of October 19, 2015) for participants in Group 4 (10 mg/kg of VRC01) and Group 5 (30 mg/kg) of HVTN 104. The number of study participants with samples assayed at each time point is shown on the X axis of each graph. As expected, trough levels following the second infusion are somewhat higher than following the first infusion. The median antibody concentration in the 10 mg/kg group is above 10 mcg/mL for approximately 37 of the 56 days (66%) following the second infusion with a median trough concentration of 4.6 mcg/mL (25-75% interquartile range 2.6 – 6.3). For the 30mg/kg group the median trough level is 9 mcg/mL (25-75% interquartile range 6.5 – 9.4).

These levels are quite similar to those modeled for the study and they show the desired overlap in concentrations achieved with the two doses selected for the study.

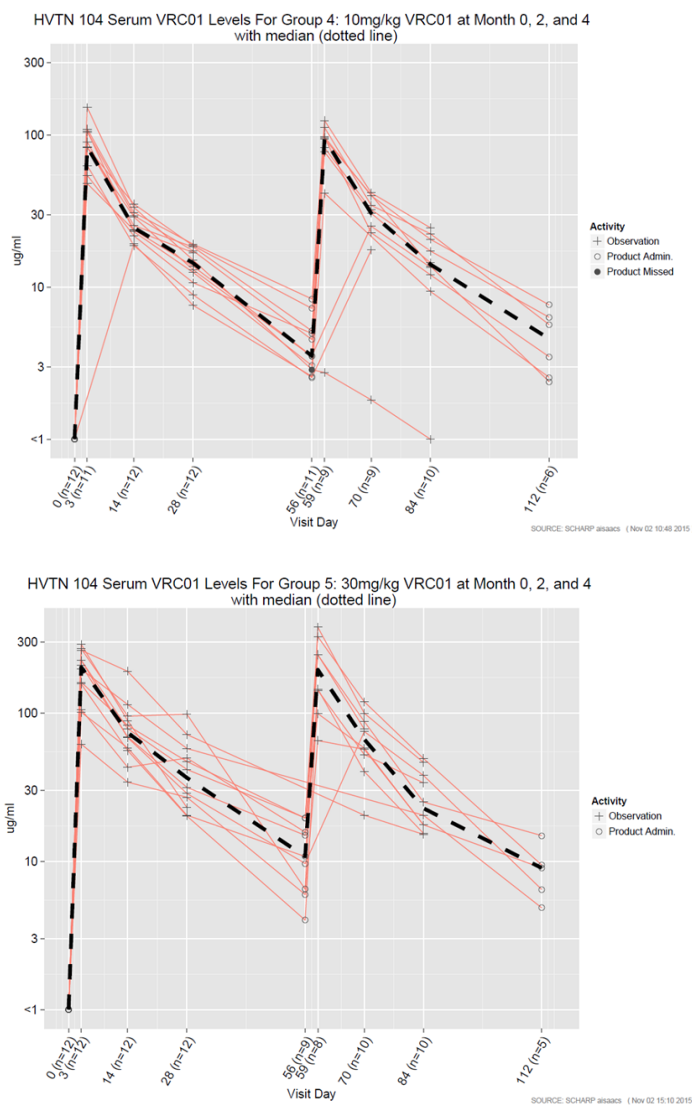


Figure 2-9 VRC01 serum levels through month 4 observed in HVTN 104 Group 4 (10mg/kg IV) and Group 5 (30mg/kg IV)

2.9.4 Safety summary of VRC01

As of February 23, 2016, approximately 130 adult participants received one or more VRC01 administrations, including 23 in VRC 601, 23 in VRC 602 (5 additional participants received placebo), and 84 in HVTN 104 (4 additional participants received placebo). 249 VRC01 infusions and 208 SC injections were given in HVTN 104.

Cumulatively, there have been no expedited safety reports to the FDA or study safety pauses for adverse events and no reactions during the VRC01 or

placebo/control product administration that resulted in an incomplete administration.

VRC01 SC or IV administrations are generally associated with mild or moderate local reactions of pruritus, redness, and pain/tenderness, which resolve within a few minutes to a few hours after the administration is completed. When present, most systemic reactions after administration of VRC01 SC or IV are mild and include: malaise, myalgia, headache, chills, nausea, and joint pain.

Unsolicited AEs of grade 3 or higher severity and deemed related to study product have not been reported.

Other AEs attributed to study product administration have included mild or moderate AST elevation, alanine aminotransferase (ALT) elevation, creatinine elevation, and decreased neutrophil count. Mild or moderate elevated transaminases were reported in 4 of 21 (19%) HIV-infected participants in VRC 601 (all of whom were taking ARVs). These laboratory changes resolved spontaneously and did not require discontinuation of study product administration. Among HIV-uninfected participants in VRC 602 or HVTN 104, 1 participant had grade 1 (mild) transiently elevated ALT assessed as possibly attributed to VRC01 in the VRC 602 study and 2 participants had grade 1 (mild) transiently elevated ALT/AST values assessed as related to VRC01 in HVTN 104. These 3 participants all received VRC01.

In the HVTN 104 trial, there were 3 product discontinuations for AEs, 2 of which were deemed related to study product infusion or injection. One discontinuation was for a 20-minute episode of chest tightness occurring approximately 25 minutes after SC injection of placebo in a participant who is a chronic smoker on nicotine replacement while smoking. One discontinuation was in a participant who reported a generalized rash that began three days after SC injection of VRC01, and resolved within 4 hours with ibuprofen and the application of an over-the-counter non-steroidal cream. The third discontinuation was in a young, otherwise healthy participant who experienced a brief episode of syncope, deemed not related to study product, approximately 4 hours after IV infusion of VRC01. In addition, one person in HVTN 104 had study product discontinued due to pregnancy occurring during the trial.

Overall, VRC01 administration in the dose range from 10 to 40 mg/kg IV and at 5 mg/kg SC has been assessed as well-tolerated and safe for further evaluation.

2.9.5 Particle formation

VRC01 is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C. For additional information, see the IB.

2.10 Potential risks of study products and administration

In a preclinical study performed in rats, there was a small dose-dependent, but transient, increase in AST and ALP, but not in ALT following IV administration. In rats, there were no histopathology findings following IV administration.

Thus far in VRC 601, VRC 602, and HVTN 104 there have been no SAEs deemed related to study product (see Section 2.9.4). Administration of mAb may have a risk of immune reactions such as acute anaphylaxis, serum sickness, and the generation of auto-reactive antibodies; however, these reactions are rare and more often associated with mAbs targeted to human proteins or with the use of murine mAbs, which would have a risk of human anti-mouse antibodies [106]. In this regard, as VRC01 is targeted to a viral antigen and is a human mAb, it is expected to have a low risk of such side effects.

Typically, the side effects of mAbs are mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, or chest pain. Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections [108]; however, this is not expected to be a risk for a mAb targeted to a viral antigen.

It is known from published experience with human mAbs directed against the cell surface targets on lymphocytes that infusion of a mAb may be associated with cytokine release, causing a reaction known as cytokine release syndrome [109]. Cytokine release syndrome and other immune reactions such as tumor lysis syndrome have been observed with administration of chimeric and humanized mAb [108]. Most infusion-related events occur within the first 24 hours after beginning administration. Specifically, with regard to cytokine release syndrome reactions, these most commonly occur within the first few hours of beginning the infusion and are more common with the first mAb infusion received. This is because the cytokine release is associated with lysis of the cells targeted by the mAb and the burden of target cells is greatest at the time of the first mAb treatment. With licensed therapeutic mAbs, cytokine release syndrome is managed by temporarily stopping the infusion, administering histamine blockers, and restarting the infusion at a slower rate [110]. Severe reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are infrequent and more often associated with mAbs targeted to human proteins or with a non-human mAb, such as a murine mAb [108].

Delayed allergic reactions to a mAb may include a serum sickness type of reaction, which is characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after exposure to the mAb and are noted to be more common with chimeric types of mAb [108]. Serum sickness has not been described with administration of licensed fully human mAbs.

There are several FDA-licensed mAbs for which reactions related to the rate of infusion have been described. Some symptoms may be treated by slowing or stopping the infusion.

Other side effects of licensed mAbs include infections, thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity [108].

The HVTN laboratory tested plasma from HIV-uninfected individuals that was spiked with VRC01 in a range of concentrations that encompasses those likely to be observed in this clinical trial. VRC01 did not cause a reactive test result using several standard antibody-based HIV-1/2 diagnostic tests used in the US. However, VRC01 is an antibody to an HIV protein, so, it may be theoretically possible for a standard antibody-based HIV diagnostic test to detect VRC01 for a short time period postinfusion or postinjection. This has not been observed in clinical studies to date.

Risks of Blood Drawing: Blood drawing may cause pain and bruising and may, infrequently, cause a feeling of lightheadedness or fainting. Rarely, it may cause infection at the site where the blood is taken. Problems from use of an IV for blood drawing are generally mild and may include pain, bruising, minor swelling, or bleeding at the IV site and, rarely, infection, vein inflammation (phlebitis), or blood clot.

Risks of IV Infusion: The placement of an IV catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized through the use of aseptic techniques during product preparation and administration.

3 Objectives and endpoints

3.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion in sub-Saharan African women

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy in sub-Saharan African women

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

3.2 Secondary objectives and endpoints

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available post-HIV-infection serum samples

3.3 Exploratory objectives

Exploratory objective 1:

To assess use of FTC/TDF in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

4 Statistical considerations

4.1 Outline of the statistical considerations section

The statistical considerations section is organized as follows. Section 4.2 states the primary and secondary efficacy objectives in terms of the target prevention efficacy (PE) parameters that are estimated in the trial, and describes the hypothesis tests regarding these efficacy parameters. Section 4.3 summarizes a statistical rationale for using a 3-arm design, which adds to the scientific rationale provided in Section 2.4. Section 4.4 describes sample size and power considerations for the primary efficacy objectives, which justify the sample size of the trial. Section 4.4 also provides operating characteristics of the trial design for addressing the primary efficacy objective. Section 4.5 describes statistical power available for the secondary objective that compares PE between the two mAb dose groups. Section 4.6 describes statistical power available for detecting safety problems of the mAb in terms of SAEs. Section 4.7 summarizes the approach to monitoring the trial including interim analysis reports provided to the DSMB. Sections 4.8, 4.9, and 4.10 describe ARV assessments, randomization, and blinding, respectively. Section 4.11 describes the approach to statistical analysis, ordered first by the approach to the analysis of PE, and secondly by the approach to the assessment of correlates of protection.

4.2 PE parameters for measuring mAb efficacy and associated primary and secondary hypothesis tests

Let PE denote the overall PE of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. This PE parameter is defined as

$$PE = [1 - \text{Cumul. incid. ratio (pooled mAb grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%,$$

where the cumulative incidence ratio is the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive the mAb divided by the probability of HIV-1 diagnosis by the Week 80 visit for participants assigned to receive control. PE is the target parameter for the primary analysis of overall PE.

The primary analysis tests the null hypothesis

$$H_0: PE = 0\% \text{ versus the alternative hypothesis } H_1: PE \neq 0\%$$

using a 2-sided $\alpha = 0.05$ level test that accounts for sequential monitoring for potential harm, non-efficacy, and high efficacy.

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall PE of the 10 mg/kg mAb group and let PE30 be the overall PE of the 30 mg/kg mAb group, defined as

$PE_{10} = [1 - \text{Cumul. incid. ratio (mAb-10 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%$

and

$PE_{30} = [1 - \text{Cumul. incid. ratio (mAb-30 mg/kg grp/control) of HIV-1 Dx by 80 Wks}] \times 100\%$.

Secondary analyses test the null hypotheses

$H_0: PE_{10} = 0\%$ versus the alternative hypothesis $H_1: PE_{10} \neq 0\%$

and

$H_0: PE_{30} = 0\%$ versus the alternative hypothesis $H_1: PE_{30} \neq 0\%$

using 2-sided $\alpha = 0.05$ level tests. Both unadjusted p-values and Holm-Bonferroni p-values will be reported for each of the individual dose versus placebo group analyses.

In addition, the following secondary analyses of PE are conducted:

- Assess a dose-response effect by testing the null hypothesis
 $H_0: \text{Cumul. HIV-1 incidence by 80 Wks equal in the 3 groups}$ versus $H_1: 0\% \leq PE_{10} \leq PE_{30}$ with at least one strict inequality
- Test the complete null hypothesis that the HIV-1 incidence is the same in the three treatment groups versus the alternative hypothesis that there are some differences
- Test for different HIV-1 incidence between the two mAb groups, where a finding of PE_{30} significantly greater than PE_{10} would demonstrate that assignment to a higher mAb dose level causes higher PE

4.3 Statistical rationale for the 3-arm design compared to a 2-arm design

An alternative design would compare a single dose and schedule of the VRC01 mAb versus control. However, the 3-arm design allows addressing additional scientific questions and improves the assessment of correlates of protection, without requiring more participants by virtue of the primary analysis being based on the pooled mAb groups versus control. Specifically, consider a 2-arm design with 2:1 allocation to a single dose of VRC01 versus placebo, compared to the 3-arm design in the protocol with 1:1:1 allocation. For scenarios where the average of PE_{10} and PE_{30} equal PE set to a number greater than 0 and less than 1, power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ is very similar between the two trial designs, for the same total number of study participants. By providing results

about estimated PE10 and estimated PE30 as well as about pooled estimated PE, the trial provides data for modeling of how PE would change given a new dose and/or schedule.

A second advantage of the 3-arm design is that it allows a direct assessment of the causal effect of different mAb infusion doses on HIV-1 incidence based on randomization of treatment assignments (a so-called ‘group-level’ correlate of protection), which can directly prove the concept that a higher mAb dose causes a greater level of protection. In contrast, with a 2-arm design the association between mAb marker characteristics and the level of PE can only be inferred with non-randomized epidemiological analysis approaches for which the results cannot be guaranteed to be free from postrandomization selection bias [111,112]. That is, without a randomization to multiple mAb interventions a result that a mAb characteristic is associated with reduced incidence of HIV-1 infection may not imply that mAb recipients with the characteristic have a higher level of PE. For instance, the implication may fail if participants tend to have fewer HIV-1 exposures during the few weeks after infusion visits compared to during the few weeks before infusion visits, which could possibly occur related to the counseling and informed consent process. Or, the implication may fail if the mAb characteristic marks an intrinsic HIV-1 susceptibility factor that is not caused by administration of the mAb [113-115]. A third advantage of the 3-arm design is that the random assignment of two mAb doses creates greater inter-individual variability in mAb characteristics, which improves statistical power for the assessment of individual-level correlates of protection.

In sum, the dose-response 3-arm design has the advantages of allowing more insightful and rigorous inferences about causal effects of the mAb and greater resolution of correlates of protection, and allows addressing the additional question of whether a higher dose confers greater PE than a lower dose.

4.4 Sample size calculations for testing for overall PE (Primary objective 2)

The trial is designed to have 90% power to test

$H_0: PE \leq 0\%$ versus the alternative hypothesis $H_1: PE > 0\%$

if the level of overall pooled PE is 60% (with a 1-sided 0.025 α -level test); the design fits the paradigm of an intermediate-sized phase 2b screening efficacy trial proposed for HIV-1 vaccine efficacy trials by Rida, Fleming et al [116].

The sample size calculations are based on the power of a 1-sided 0.025-level Wald test for comparing log-transformed cumulative incidences of HIV-1 infection by the Week 80 visit between randomized groups, in the presence of the sequential monitoring described below. Power is computed based on simulating 10,000 efficacy trials under assumptions described below using the R package seqDesign.

4.4.1 Assumptions of the sample size calculations including sequential monitoring for PE

The following assumptions are made for the sample size calculations:

- 10% annual dropout incidence in each of the three study groups
- 27 month uniform accrual with halved accrual during the first three months (approximating current accrual projections)
- visits every 4 weeks for HIV-1 diagnostic tests through Week 80 and HIV-1 status at Week 80 is known
- 4.0% annual HIV-1 incidence in the control group
- For each of the mAb treatment groups, average PE versus control within an 8-week infusion interval is assumed to be the same for each of the 10 infusion intervals
- Sequential monitoring of the mAb groups versus control to stop early for:
 - Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring adjusted 90% CI lying below 0%]
 - Non-efficacy [Establish that PE (pooled over the mAb groups) $\leq 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
 - High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

With the exception of the potential harm monitoring, the sequential monitoring of PE does not use critical values adjusted for the number of analyses. Examination of the design operating characteristics (reported in the figures and tables below) was used to ensure that this approach provides a fitting trade-off of the control of false negative and false positive error rates.

Justification for the incidence assumptions is provided in Section [4.4.6](#).

We also show power calculations allowing for lower levels of HIV-1 incidence. In particular, we show power calculations assuming 3.3% annual HIV-1 incidence in the control group, which would account for lower than expected incidence rates due to increased PrEP usage.

4.4.2 Power curves and operating characteristics of the design (Primary objective 2)

Required sample sizes to achieve 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of PE are determined based on 1-sided 0.025 level Wald tests as described above. The power calculations are repeated for a

range of sample sizes to determine the required sample size to achieve 90% power as reported in [Figure 4-1](#). These power calculations are conducted using the open source R package seqDesign developed by the protocol statisticians [117], which computes power based on simulating many thousands of efficacy trials, applying the sequential monitoring procedures to each trial, and computing power as the fraction of the trials where the 1-sided 0.025-level Wald test rejects the null hypothesis. The calculations are based on a large number of simulated efficacy trials.

[Figure 4-1](#) shows the total sample size required to have 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for different values of $PE = PE_{10} = PE_{30}$. The results show that about $N = 1800$ total participants are needed to achieve 90% power to detect $PE = 60\%$; the sample size $N = 1900$ total participants (~634 per arm) is selected to build in a provision of robustness to the control group annual incidence being lower than 4.0%.

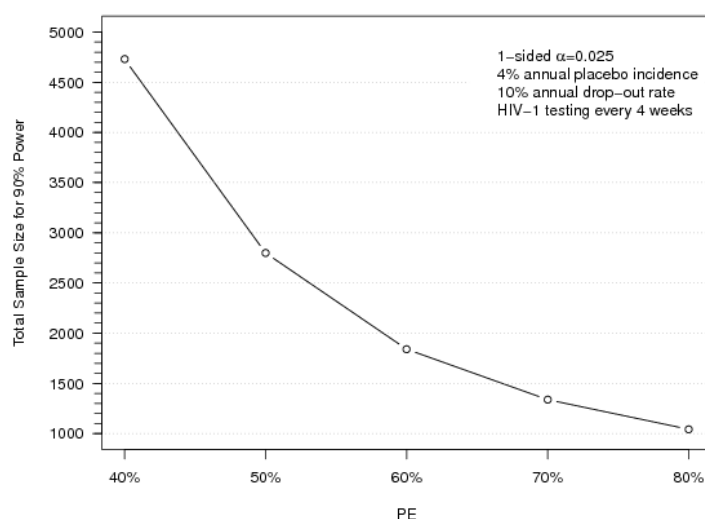


Figure 4-1 Total sample size for 90% power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

[Table 4-1](#) shows power available to reject the null hypothesis under different levels of true PE.

Table 4-1 Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ under different effect sizes $PE = PE_{10} = PE_{30}$

	Unconditional Power ($\times 100$)
0%	2.7
10%	7.4
20%	18.7
30%	37.0
40%	60.5
50%	82.1
60%	95.1
70%	99.4
80%	>99.9
90%	>99.9
95%	>99.9

The power calculations for the primary analysis of prevention efficacy were done assuming $PE_{10} = PE_{30}$, and it is of importance to also understand power available in the primary analysis in the event that PE_{10} differs from PE_{30} . Power for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ when PE equals a fixed constant PE_0 greater than 0 and less than 1 is very similar for different values of (PE_{10}, PE_{30}) subject to the constraint of average value $(PE_{10} + PE_{30})/2 = PE_0$. For example, power to test H_0 vs. H_1 is very similar for $(PE_{10}, PE_{30}) = (60\%, 60\%)$ and for $(PE_{10}, PE_{30}) = (30\%, 90\%)$. This result attains because all of these scenarios have the same number of expected HIV-1 infection events among study participants assigned to receive VRC01. Power tends to be slightly greater for differential scenarios like $(PE_{10}, PE_{30}) = (30\%, 90\%)$ compared to the equal scenario $(PE_{10}, PE_{30}) = (60\%, 60\%)$, because the hypothesis testing procedure stratifies by VRC01 dose group, gaining efficiency by accounting for a baseline variable that predicts HIV infection. Therefore, the trial is powered to detect the design alternative of a dose-pooled VRC01 efficacy PE equal to 60%, regardless of whether VRC01 efficacy differs by dose group.

4.4.3 Additional operating characteristics of the design for assessing primary objective 2

For the selected sample size ($N = 1900$), [Figure 4-2](#) shows the power curves for rejecting $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for a range of fixed values of the pooled PE . The power for rejecting H_0 when the HIV-1 incidence rate is lower than projected is included in the figure. At the lower incidence of 3.3%, there is 90.5% power to detect $PE = 60\%$. Section [4.4.6](#) describes the rationale for the incidence assumptions in this trial.

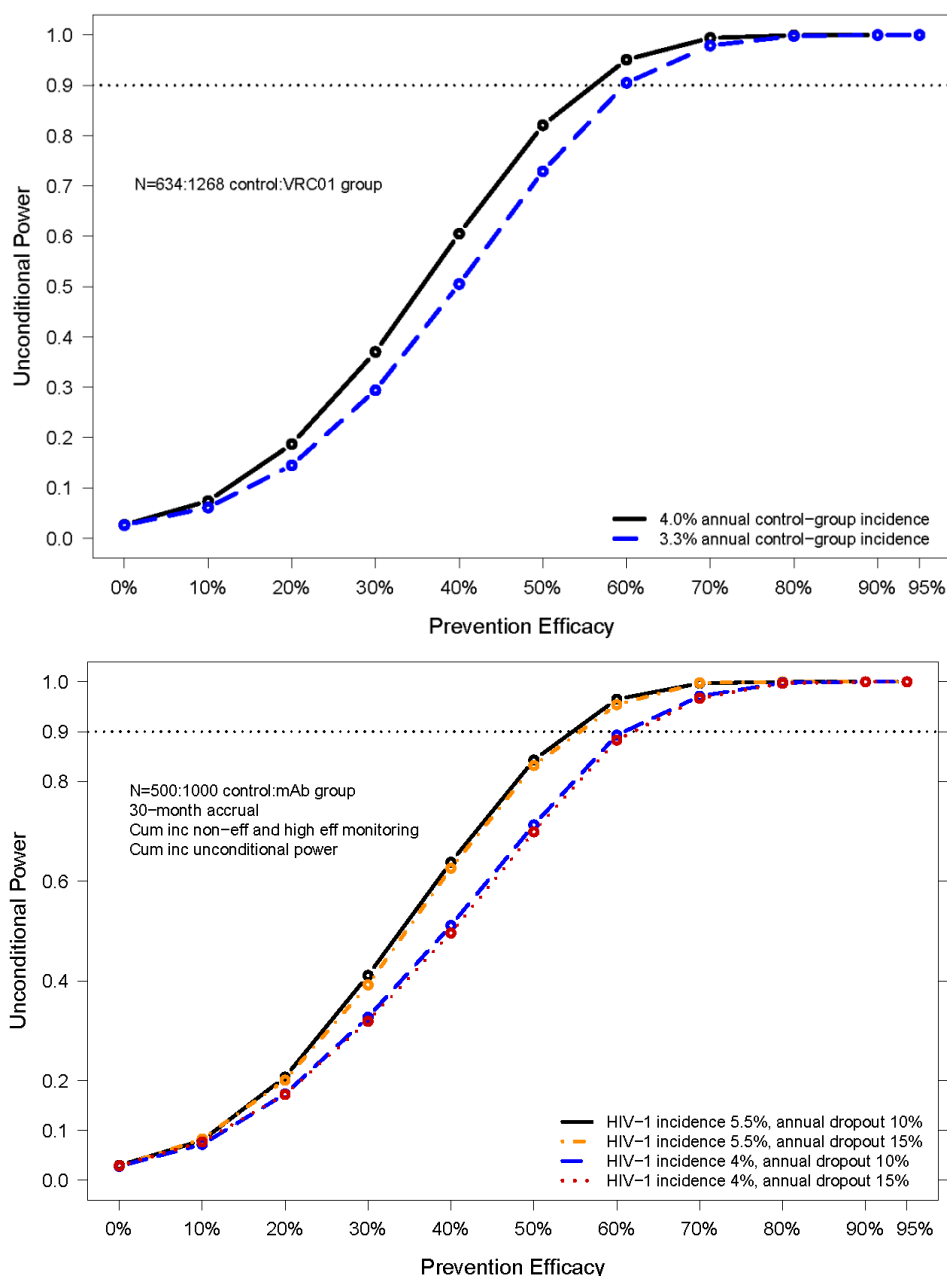


Figure 4-2 Unconditional power to reject $H_0: PE \leq 0\%$ in favor of $H_1: PE > 0\%$ for a range of fixed values of pooled PE based on primary assumptions for HIV-1 incidence and dropout rate. A power curve is also shown for a lower than expected HIV-1 incidence rate.

4.4.4 Additional operating characteristics of the primary analysis accounting for the sequential monitoring

For the selected sample size ($N = 1900$), [Figure 4-3](#) shows probabilities of reaching each possible trial monitoring outcome, pooling over the two mAb treatments (under the primary assumptions about HIV-1 incidence and dropout rates). More specifically, the monitoring outcomes include potential harm, non-efficacy, and high efficacy. [Table 4-2](#) provides the same information in tabular form. In addition, the figure and table show unconditional power in the primary

analysis to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$.

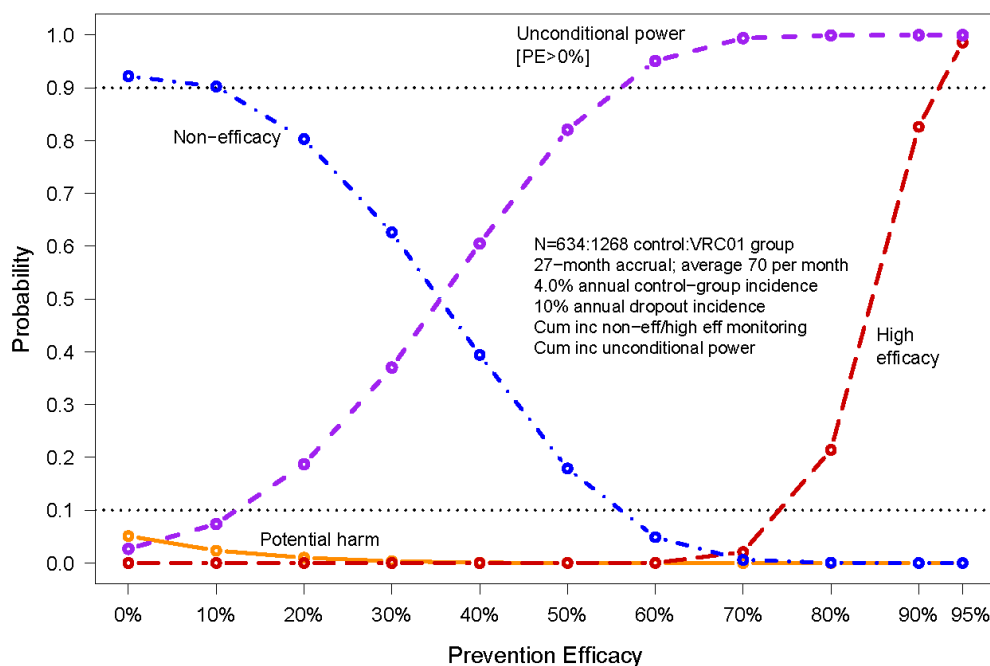


Figure 4-3 Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the primary null hypothesis $H_0: PE \leq 0\%$ with 634 control recipients and 1268 mAb recipients (1-sided 0.025-level tests)

Table 4-2 Probabilities (x 100) of reaching each possible trial monitoring outcome, and unconditional power (x 100) to reject the null hypothesis $H_0: PE \leq 0\%$ in favor of the alternative hypothesis $H_1: PE > 0\%$, pooling over the two mAb groups (1-sided 0.025-level tests)

		Weed Out at Interim Analysis			Unconditional Power PE > 0%
PE	HR	Potential Harm PE < 0%	Non-Efficacy PE < 40%	High Efficacy PE > 70%	
	3.0	95.5	4.5	0.0	0.0
	2.5	87.7	12.3	0.0	0.0
	2.0	67.7	32.3	0.0	0.0
	1.5	34.3	65.7	0.0	0.0
0%	1.0	5.1	92.2	0.0	2.7
10%	0.9	2.4	90.3	0.0	7.4
20%	0.8	1.0	80.3	0.0	18.7
30%	0.7	0.3	62.6	0.0	37.0
40%	0.6	0.1	39.4	0.0	60.5
50%	0.5	0.0	17.9	0.0	82.1
60%	0.4	0.0	4.9	0.0	95.1
70%	0.3	0.0	0.6	2.1	99.4
80%	0.2	0.0	0.0	21.4	>99.9
90%	0.1	0.0	0.0	82.6	>99.9
95%	0.0	0.0	0.0	98.6	>99.9

N = 634:1268 Control:mAb group

4.0% annual incidence in the Control group

10% annual dropout

Cumulative incidence-based non-efficacy monitoring

Cumulative incidence-based high-efficacy monitoring

Cumulative incidence-based unconditional power

Table 4-3 shows the numbers of HIV-1 infection endpoints during the trial expected under the null hypothesis scenario $PE = PE_{10} = PE_{30} = 0\%$ and under the design alternative hypothesis scenario $PE = PE_{10} = PE_{30} = 60\%$. Under the design alternative hypothesis scenario, the calculations show that 35 HIV-1 infection endpoints are expected in the control group and 28 HIV-1 infection endpoints are expected in the two mAb groups combined after 80 weeks of follow-up.

Table 4-3 Cumulative number of HIV-1 infection endpoints over 80 weeks of follow-up under the null hypothesis scenario $PE_{10} = PE_{30} = 0\%$ and under the design alternative hypothesis scenario $PE = PE_{10} = PE_{30} = 60\%$. Medians are computed based on simulating a large number of efficacy trials.

PE ₁₀ = PE ₃₀	Weeks since first person in	Median number of control endpoints	Median number of pooled mAb group endpoints
0%	0	0	0
0%	26	1	1
0%	52	4	8
0%	78	10	20
0%	104	18	35
0%	130	23	47
0%	156	26	51
0%	182	26	53
0%	197	26	54
60%	0	0	0
60%	26	1	0
60%	52	4	3
60%	78	10	8
60%	104	18	14
60%	130	26	21
60%	156	31	25
60%	182	34	28
60%	197	35	28

4.4.5 Power curves for secondary hypothesis tests about PE in each mAb group

Figure 4-4 shows unconditional power to reject the null hypothesis $H_0: PE_{10} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{10} > 0\%$ (or, equivalently, the null hypothesis $H_0: PE_{30} \leq 0\%$ versus the alternative hypothesis $H_1: PE_{30} > 0\%$), where PE_{10} and PE_{30} measure prevention efficacy in each mAb group separately.

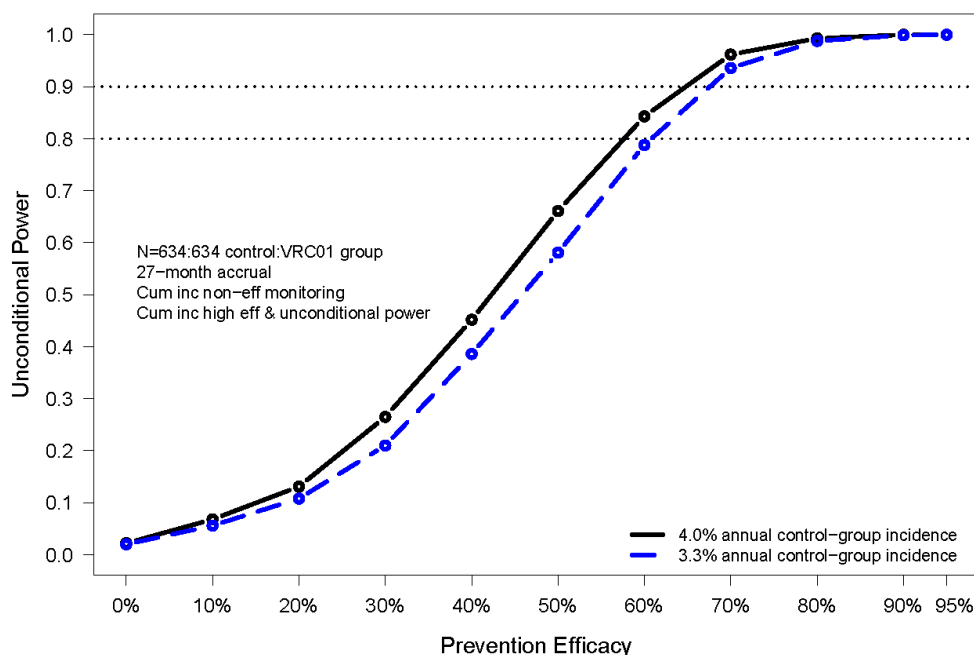


Figure 4-4 Unconditional power to reject $H_0: PE_{10} \leq 0\%$ in favor of $H_1: PE_{10} > 0\%$ (or $H_0: PE_{30} \leq 0\%$ in favor of $H_1: PE_{30} > 0\%$) based on primary assumptions about HIV-1 incidence rate and dropout rate. A power curve is also shown for a lower than expected HIV-1 incidence rate.

4.4.6 Rationale for the HIV-1 incidence assumptions

The assumption of 4.0% annual HIV-1 incidence for the control group is based on recent data directly measuring HIV-1 incidence in women at several African sites [6,61,64-67,81,82,118]. The overall annual incidence rate in the VOICE study was 5.7%, which pools over all intervention groups given the similar incidence rates and the lack of significant differences. The annual incidence rate of female control recipients in the Phambili study, at 5.1%. The Fem-Prep and ASPIRE studies had annual incidence rates of 5.0% and 4.5%, respectively, in the control groups. The FACTS-001 trial showed no efficacy and the annual incidence was 4.0% for both study arms.

The total sample size $N=1900$ builds in a conservative margin, where the smallest control group annual incidence under which there is at least 90% power to detect $PE = 60\%$ is 3.3%. Moreover, power is 81.9% to detect $PE = 60\%$ if the control group annual incidence is 2.56%. This scenario of 2.56% annual incidence is consistent with the following scenario in which many study participants choose to use Truvada PrEP: 60% of person-years at-risk are without PrEP use and a 4.0% control group annual incidence, and the other 40% of person-years at-risk are with PrEP use at 90% PrEP efficacy and thus a 0.4% control group annual incidence. In this scenario, an assumption of 75% (instead of 90%) PrEP efficacy yields the control-group annual incidence of 2.8% (instead of 2.56%).

Based on a synthesis of the above-cited references using control arms or active arms in trials that showed no efficacy, we assume that the background annual incidence of HIV-1 in sub-Saharan African women in the absence of any PrEP

use is 5.1%. It is difficult to predict the degree of PrEP use that will occur in sub-Saharan African women. Given that the South African Medicines Control Council (MCC) approved fixed-dose emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for use as PrEP only recently (December 2015) and the drug is not yet available in the public sector on which the vast majority of South Africans depend for health care and pharmaceuticals. While the government of South Africa is committed to rolling PrEP out as part of its HIV prevention efforts and is currently undertaking a limited number of narrowly targeted demonstration projects, when PrEP will be available more broadly in South Africa is unclear. The situation is equally uncertain in the other sub-Saharan countries in which this trial will be conducted. Assuming 15% of the PYRs under PrEP use with 90% (75%) PrEP efficacy leads to 4.4% (4.5%) control-group annual incidence. This protocol assumes conservatively 4.0% annual incidence in the control group.

Higher than expected use of PrEP will be reflected in lower than expected annual incidence rates. As shown in [Figure 4-2](#), however, the trial would still provide enough statistical information to be powered to detect highly relevant prevention efficacy effect sizes if annual incidence rates are lower than we have estimated here due to higher than expected use of PrEP.

4.5 Power for the secondary analysis comparing HIV-1 incidence between the 10 mg/kg mAb group versus the 30 mg/kg mAb group

[Table 4-4](#) reports power calculations for comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. The calculations assume the scenarios for true values of PE10 and PE30 indicated in the first two columns of the table. The results show that the study is moderately powered to detect large differences (eg, 65.6% power to discriminate 30% vs 70% PE) but may miss moderate differences (eg, 37% power to discriminate 30% vs 60% PE). In contrast, the study has high power to correctly select the best mAb dose group given moderate efficacy differences. Specifically, if the true PE30 is moderately greater than the true PE10, then there is high probability that the estimated PE30 would be greater than the estimated PE10, such that the 30 mg/kg mAb dose group would be selected.

Table 4-4 Statistical power for comparing the 10 versus 30 mg/kg mAb groups: Power to select the best mAb group and power to correctly select the best mAb group

PE10	PE30	Power to Select Best mAb Dose Group [§]	Power to Detect PE10 Different from PE30 [#]
20%	60%	84.1	55.2
30%	60%	82.4	37.7
40%	60%	77.7	19.0
30%	70%	96.0	65.6
50%	85%	99.0	72.5

[§] Probability that the mAb dose group that is truly better (the 30 mg/kg dose group in the scenarios considered in the table) is correctly selected based on the point estimate for PE30 exceeding that for PE10. Specifically, correct selection entails that the estimated PE30 is greater than the estimated PE10 and that PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

[#] Cumulative hazard-based 2-sided Wald tests comparing HIV-1 incidence between the 10 mg/kg and 30 mg/kg mAb groups. Rejection of the null hypothesis requires that PE30 is significantly > 0% (1-sided $\alpha = 0.025$)

4.6 Sample size calculations for safety

We consider the statistical power of Fisher's exact test to detect a higher rate of SAEs in a mAb group (Group 1 or 2 with $n = 634$) versus the control group (Group 3 with $n = 634$). Based on HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE. The tests use a 2-sided α -level of 0.05. This level does not correct for the 4 comparisons; however this is appropriate because it is desirable to maximize power to detect a safety problem. For the safety calculations, we assume no missing data as almost all participants will have some follow-up data for safety.

To describe the precision of the study to characterize differences in SAE rates between groups, [Table 4-5](#) shows 2-sided 95% CIs for different levels of observed differences (mAb group-control) of event rates between a mAb group of size $n_1 = 634$ (or the combined mAb groups $n_2 = 1268$) and a control group of size $n_0 = 634$.

Table 4-5 Two-sided 95% CIs for different observed event rate differences of safety endpoints between the mAb recipient and control groups*

Observed event rate in controls ($n_0 = 634$)	Observed event rate in single mAb group ($n_1 = 634$)	Observed event rate in combined mAb groups ($n_1 = 1268$)	Rate difference (mAb group – control)	95 % CI ($n_1 = 634$)	95% CI ($n_1 = 1268$)
0%	2%	2%	2%	(0.0116, 0.0341)	(0.0136, 0.0293)
	4%	4%	4%	(0.0273, 0.0582)	(0.0305, 0.0523)
	10%	10%	10%	(0.0790, 0.1258)	(0.0847, 0.1177)
	20%	20%	20%	(0.1707, 0.2329)	(0.1789, 0.2229)
2%	2%	2%	0%	(-0.0164, 0.0164)	(-0.0155, 0.0126)
	4%	4%	2%	(0.0013, 0.0403)	(0.0032, 0.0351)
	10%	10%	8%	(0.0553, 0.1075)	(0.0598, 0.1000)
	20%	20%	18%	(0.1482, 0.2114)	(0.1554, 0.2049)
4%	2%	2%	-2 %	(-0.0403, -0.0013)	(-0.0394, -0.0044)
	4%	4%	0%	(-0.0222, 0.0222)	(-0.0205, 0.0177)
	10%	10%	6%	(0.0325, 0.0891)	(0.0365, 0.0822)
	20%	20%	16%	(0.1261, 0.1957)	(0.1327, 0.1867)

*95% CIs are computed using the method of Miettinen and Nurminen [119]. Entries are bolded where significantly more events are observed among mAb recipients than among control recipients based on the 95% CI.

[Figure 4-5](#) shows the power to detect an elevated SAE rate as a function of the true rate in the mAb group under consideration.

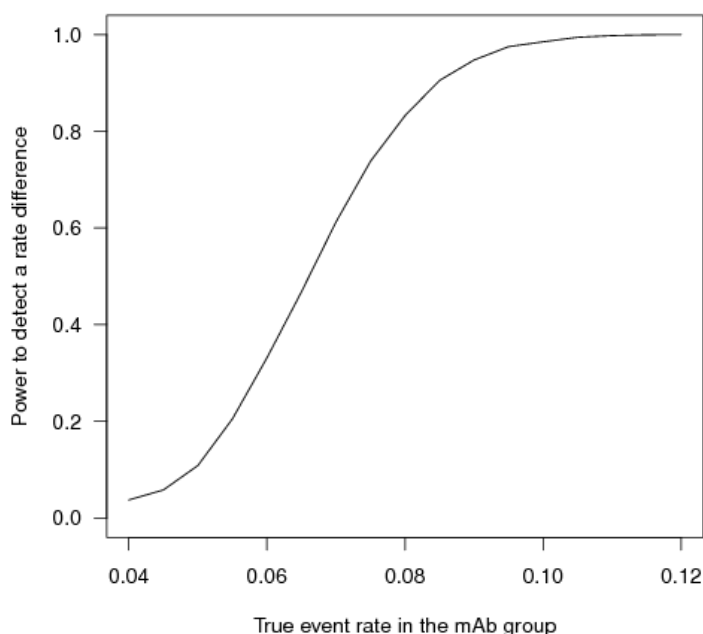


Figure 4-5 Power to detect a greater SAE rate in a mAb group versus the control group given a 4% SAE rate in the control group (2-sided 0.05-level test)

Figure 4-5 shows that there is 80% power to detect a higher SAE rate in a mAb arm if the true SAE rate is 7.8% and 90% power if the true rate is 8.5%.

4.7 Monitoring of the trial

4.7.1 Role of the Data and Safety Monitoring Board (DSMB)

The study DSMB will review study data at 6-monthly interim analyses to evaluate safety, integrity, and efficacy of the ongoing trial. Following each DSMB meeting, the DSMB reports to the Oversight Committee (OC) a summary of the trial review, which may include recommendations to modify or terminate the trial. The DSMB is guided by a trial monitoring plan, and reviews and approves the monitoring plan before the trial initiates.

Each 6-monthly DSMB report will include a complete analysis of safety data. If a total of $N = 20$ participants reach the Week 12 study visit before the first DSMB report is generated, then a safety report based on these data will be provided to the DSMB as soon as possible and before the first DSMB meeting. The contents of the early report are the same as the contents in the scheduled 6-monthly DSMB reports.

In addition, as soon as 10 grade 2 or higher AEs occur, a report will be generated describing these AEs and will be provided to the DSMB. The DSMB reports will also tabulate occurrence of SAEs, and of AEs judged related to product, accounting for the number of infusions received.

4.7.1.1 Sequential monitoring for potential harm, non-efficacy, and high efficacy

The trial uses sequential monitoring of the mAb groups versus control to stop early for:

- Potential harm [Establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring-adjusted 90% CI lying below 0%]
- Non-efficacy [Establish that PE (pooled over the mAb groups) $< 40\%$ based on a 2-sided 95% nominal CI lying below 40%]
- High efficacy [Establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal CI lying above 70%]

The sequential monitoring is based on CIs in order that the result of the study that would be reported would convey evidence supporting the conclusion of potential harm, non-efficacy, or high efficacy. Freidlin, Korn, and Gray [120] discuss a rationale for this approach to non-efficacy monitoring. The sequential monitoring for potential harm is based on monitoring-adjusted 1-sided 0.05-level tests (instead of 1-sided 0.025-level tests) for prudence to protect the safety of study participants (ie, less precision is required to meet a guideline for potential harm than to meet guidelines for non-efficacy or high-efficacy). Once non-efficacy monitoring commences, the potential harm monitoring after each infection ceases, as the non-efficacy monitoring now provides the function of detecting an elevated rate of HIV-1 infection. The non-efficacy monitoring is supplemented with conditional power calculations that report estimates of the probability of rejecting the null hypothesis of zero PE under different assumptions about the estimated PE if the trial were to continue to the end. The sequential monitoring plan is summarized in [Table 4-6](#) and [Figure 4-6](#).

Table 4-6 Summary of sequential monitoring of PE

Monitoring Type	Hypotheses	Testing Approach	Size of Test	Stopping Boundary	Timing of Interim Analyses
Potential Harm	H0: PE $\geq 0\%$ vs H1: PE $< 0\%$	Exact 1-sided binomial test of the fraction of infections assigned to receive the mAb	Specified in the monitoring plan	Near-constant 1-sided p-value cut-off controlling the FWER at $\alpha = 0.05^*$	After every infection from 20 th total until first non-efficacy analysis
Non-Efficacy	H0: PE $\geq 40\%$ vs H1: PE $< 40\%$	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI below 40% supplemented with conditional power (specified in the monitoring plan)	6-monthly starting based on an event-driven trigger specified in the monitoring plan
High Efficacy	H0: PE $\leq 70\%$ vs H1: PE $> 70\%$	2-sided Wald test and 1:1 corresponding 2-sided 95% CI	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI above 70%	6-monthly starting at the same time as for non-efficacy

* Equivalently, a monitoring-adjusted 2-sided 90% CI based on inversion of the test statistic lies below 0%. The 1-sided p-value significance threshold stopping boundaries after each infection event are specified in the study monitoring plan.

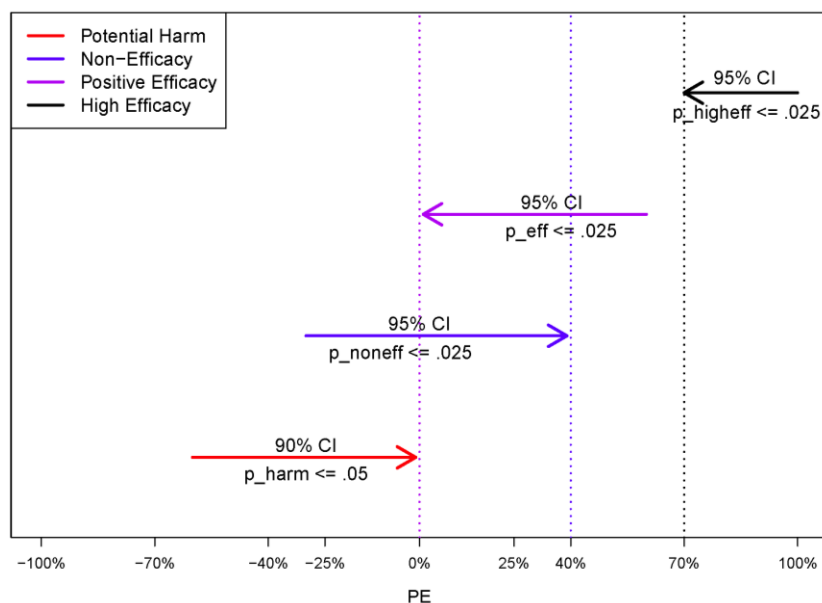


Figure 4-6 Stopping boundaries for the sequential monitoring based on 2-sided CIs (or on the corresponding 1-sided p values)

Details of the sequential monitoring plan will be provided in a separate trial monitoring plan. The sequential monitoring is closely related to what was done for the HVTN 505 HIV-1 vaccine efficacy trial [121] (background discussion in [73]).

4.7.2 Feasibility check and guideline for continuing enrollment as planned

In addition to the sequential monitoring of PE, feasibility monitoring is done for the first 120 enrolled participants. This feasibility monitoring is based on the first four 8-week intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of participants attend clinical visits and receive the infusions per the protocol. The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) supplemented by data on visit attendance, which corresponds to adherence to receipt of infusions. Additional details will be provided in the trial monitoring plan.

The feasibility monitoring based on the first 120 enrolled participants will use the following guideline for continuing enrollment as planned: continued participation by the Week 32 visit pooled over the 3 groups is greater than 80%.

If the blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is warranted.

4.7.3 Monitoring for futility to assess PE

The objective of monitoring the trial for futility to assess PE is to monitor progress toward the minimal needed target number of treatment arm-pooled HIV-

1 primary endpoint infections by the Week 80 visit in the MITT cohort. Two targets are monitored for:

1. the total number of HIV-1 infections needed to achieve the planned 90% power to detect PE = 60%, and
2. the total number of HIV-1 infections needed to achieve 50% power to detect PE = 60%,

each using a 1-sided 0.025-level Wald test of $H_0: PE \leq 0\%$ against $H_1: PE > 0\%$, assuming proportional hazards of HIV-1 infection in the pooled VRC01 and control groups. The target numbers in (1) and (2) are 57 and 21, respectively (calculated by solving equation (1) in Schoenfeld [122]). The rationale for considering the two targets is as follows: (i) if the trial cannot achieve the planned 90% power to detect PE = 60%, considerations about enrollment modification or expansion are warranted, and (ii) if the trial cannot achieve even 50% power to detect PE = 60%, considerations about completing the trial early for futility to assess PE are warranted.

Two versions of the futility monitoring report will be generated. A report provided to the DSMB will be included in 6-monthly closed DSMB reports, starting in November 2017, and will report:

- a. the estimated distribution of the total (i.e., treatment arm-pooled) number of HIV-1 infections, with corresponding power to reject $H_0: PE \leq 0\%$ using a 1-sided 0.025-level Wald test under the alternative hypothesis PE = 60% throughout the trial,
- b. the estimated probability that the total number of HIV-1 infections is ≥ 57 (target 1) with 95% credible intervals,
- c. the estimated probability that the total number of HIV-1 infections is ≥ 21 (target 2) with 95% credible intervals,
- d. the estimated distribution of the number of HIV-1 infections in each of the three treatment arms.

The distributions in (a) and (d) will also be summarized by the mean number of HIV-1 infections with a Wald 95% confidence interval. The estimation procedure for (a)–(d) will be conducted under each of the following two scenarios:

- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 60% (the design alternative), and

- the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that PE = 0% (the null hypothesis).

The reason for conducting the estimation procedure twice is that the purpose of the results for the 57 endpoint target (b) is to trigger considerations for trial modifications, whereas the purpose of the results for (c) is to trigger considerations for early trial completion due to futility, where it is desired to reach the guideline (b) more easily/readily than the guideline (c). Accordingly, the results for (b) are interpreted focusing on the prior of PE = 60%, which makes it more likely to reach a guideline than the prior of PE = 0%, and the results for the 21 endpoint target (c) are interpreted focusing on the prior of PE = 0%, which makes it less likely to reach a guideline than the prior of PE = 60%.

Furthermore, a treatment-blinded report will be generated for distribution to the OC after each DSMB meeting takes place and will report estimates listed in (a)–(c) above calculated based only on treatment-blinded data. The reported results pertaining to estimates (a)–(c) will be identical to those in the DSMB report.

While it is the primary responsibility of the OC to make decisions regarding trial operations and modifications based on the monitoring of treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. More specifically, the DSMB can evaluate the progress toward primary endpoint targets in the context of the treatment-unblinded data, and based on this review may recommend to the OC to complete the trial early due to reaching a guideline for futility to assess PE (specified below).

The monitoring for futility to assess PE includes the following guidelines for trial modifications:

- **[Guideline for enrollment modifications]** If, in the PE = 60% scenario for the prior distribution, the estimated probability of reaching at least 57 total infections is less than 25%, the Oversight Committee may consider enrollment modifications with the intention to be able to conduct the primary PE analysis with adequate power.
- **[Guideline for futility]** If, in the PE = 0% scenario for the prior distribution, the estimated probability of reaching at least 21 total infections is less than 25%, the DSMB may recommend completing the trial early based on the inability to conduct the primary PE analysis with adequate power. However, since this is a proof-of-concept trial, a high bar is desired for completing the trial early for futility, and therefore if this event occurs yet the non-efficacy monitoring has not started or the non-efficacy boundary has not been reached, then this guideline for futility also requires that the estimated PE for the pooled VRC01 vs. control arm is < 30% and the estimated PE for the VRC01 30 mg/kg vs. control arm is < 30%.

If enrollment is incomplete at the time of an interim futility analysis, then the outlined estimation procedures will use the average observed enrollment rate in approximately the last 6 months for generating future enrollment data. In addition, a Bayesian approach will be used for generating future HIV-1 incidence data, conditional on observed data to-date. More specifically, the estimates in (a)–(c) will condition on the observed to-date treatment arm-pooled HIV-1 incidence rate, whereas the estimates in (d) will condition on the observed to-date (three) treatment arm-specific HIV-1 incidence rates. All estimates in (a)–(d) will also use the observed to-date treatment arm-pooled dropout rate for generating future dropout data.

If, at any time, these guidelines for futility to assess PE are met and yet it appears that value exists in continuing the trial, the statisticians will provide the DSMB and the OC with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

4.8 Assessment of PrEP use

The use of oral FTC/TDF as PrEP (either off-study or provided in the study) may impact study outcomes (eg, by lowering HIV incidence with a loss of study power). Dried blood spot samples will be collected and stored for assessment of quantitative concentrations of intracellular TFV (see Section 9.6), using a calendar based selection of visits that will ensure representative sampling of participants across the entire visit schedule at all sites throughout the study. A detailed testing plan, specified in the study monitoring plan, has been developed to prospectively monitor FTC/TDF use during the trial to inform the DSMB, and assess the potential impact of FTC/TDF use on PE of the study product. Prevalence of PrEP will be reported both as the estimated proportion of participant visits with highly adherent PrEP use (above the concentration of TFV designated as consistent with daily dosing) and the proportion of participant visits with any detectable PrEP use (concentration of TFV above the lower limit of detection for the dried blood spot assay). Additionally, we will use knowledge of PK quantitative levels to estimate the proportion of study person years protected by highly adherent use of FTC/TDF. PrEP use measures will be reported by arm to the DSMB; in addition both the OC and the protocol team leadership will see pooled estimates of FTC/TDF use.

4.9 Randomization

The randomization sequence will be obtained by computer-generated random numbers and provided to each CRS through a Web-based randomization system. The randomization will be done in blocks to ensure balance across arms. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining security of the treatment assignments (except in emergency situations as specified in the SSP).

4.10 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know this information in order to ensure proper trial conduct. Any discussion of study product assignment between pharmacy staff and any other CRS staff is prohibited.

When a participant leaves the trial prior to study completion, the participant will be told he or she must wait until all participants are unblinded to learn his or her treatment assignment.

Emergency unblinding decisions will be made by the site investigator. If time permits, the HVTN 703/HPTN 081 PSRT should be consulted before emergency unblinding occurs.

4.11 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many infusions they received. In the rare instance that a participant receives the wrong treatment at a specific infusion visit, the Statistical Analysis Plan will address how to analyze the participant's safety data. Analyses are modified intent-to-treat (MITT) in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of blinding and the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected.

Analyses for primary endpoints will be performed using SAS and R. All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

4.11.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, efficacy, and markers of mAb characteristics for primary- and secondary-objective analyses.

4.11.2 Baseline comparability

Treatment arms will be compared for baseline participant characteristics using descriptive statistics.

4.11.3 Safety/tolerability analysis

Since enrollment is concurrent with receiving the first infusion, all participants will have received at least 1 infusion and therefore will provide some safety data.

4.11.3.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's reactogenicity will be counted once under the maximum severity for all injection visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

4.11.3.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. Formal statistical testing comparing arms is not planned since interpretation of differences must rely heavily upon clinical judgment.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

4.11.3.3 Local laboratory values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table (see Section [10.2.2](#)) will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

4.11.3.4 Reasons for infusion discontinuation and early study termination

The number and percentage of participants who discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

4.11.4 Efficacy analysis

4.11.4.1 General approach

For the statistical analysis of prevention efficacy, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Given that all or almost all participants will receive the first infusion, the analyses are MITT, where all participants HIV-1 negative at entry receiving the initial infusion are included in the analysis, participants are analyzed according to their randomized treatment assignment, and participants retrospectively determined to be HIV-1 infected at entry based on treatment blinded procedures are excluded from the analysis. Additional analyses may be performed, limited to participants who received most or all infusions per protocol.

Cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms will be estimated by a transformation of Nelson-Aalen estimators [123] for the respective cumulative hazard functions of HIV-1 infection. PE parameters will be estimated by one minus the ratio (mAb/control group) of these cumulative incidence estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported. These procedures will be used to test the hypotheses listed in Section 4.2.

As a supportive analysis for the hypotheses listed in Section 4.2, targeted maximum likelihood estimation (tMLE) will be used to estimate cumulative incidences of HIV-1 infection over time for different treatment arms and pooled treatment arms [124,125]. The Statistical Analysis Plan will describe the details of implementation of the tMLE estimators in an automated and objective fashion. PE parameters will be estimated by 1 minus the ratio (mAb group/control) of these tMLE estimators. Point estimates and 95% Wald CIs about cumulative incidence curves and PE(t) curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of HIV-1 infection over time, complementary secondary analyses will assess hazard-ratio based PE using Cox proportional hazards models with score tests stratified by VRC01 dose group for testing whether PE differs from zero. This analysis uses as the failure time the time from the most recent infusion to the estimated date of HIV infection, entered in the Cox model as a time-dependent covariate. This analysis can have increased power to detect prevention efficacy compared to the primary analysis of the cumulative incidence based parameter PE, if instantaneous prevention efficacy is higher when VRC01 concentrations are lower. Goodness-of-fit diagnostics will be applied to assess veracity of the proportional hazards

assumption. The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity of the primary analysis does not depend on the proportional hazards assumption. The Cox model will also be used for a secondary analysis of PE in subgroups defined by the level of cumulative infusion adherence over time included in the model as a time-varying covariate.

Sensitivity analyses of the primary analysis will test $H_0: PE = 0\%$ with a log-rank test and with a Gehan-Wilcoxon test stratified by VRC01 dose group. To explore potential time-variations in prevention efficacy, instantaneous prevention efficacy over time defined based on the instantaneous hazard ratio (VRC01 vs. placebo) will be estimated with pointwise and simultaneous confidence bands using nonparametric kernel smoothing [126].

4.11.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety or efficacy endpoint assessments.

4.11.6 Specific approach for assessing PE, PE10, PE30

Primary objective 2 is addressed based on comparing cumulative HIV-1 incidence between the group of participants assigned to receive the VRC01 mAb (at either dose pooling over the two doses) and the group of participants assigned to the control group, and secondarily between each individual mAb dose group and the control group. For each prevention efficacy parameter PE, PE10 and PE30, point and 2-sided 95% CI estimates will be reported, along with the 2-sided p-values for testing the respective null hypotheses (with 2-sided $p = 0.05$ the threshold for a significant effect). Unadjusted and Holm-Bonferroni p-values will be reported for testing of the secondary endpoint efficacy parameters PE10 and PE30.

4.11.7 Assessment of individual-level markers of VRC01 mAb that correlate with protection against HIV infections (Secondary objective 1)

Secondary objective 1 is addressed based on the measurement of VRC01 mAb markers over time in mAb group breakthrough HIV-1–infected cases and in a random sample of HIV-1–uninfected mAb group participants (marker subset), integrated with the genotypic and phenotypic sieve analysis of breakthrough HIV-1 viruses accounting for knowledge of the VRC01 antibody footprint. The main analyses of the secondary objective 1 pool over the two mAb doses to maximize statistical power.

The design and results requirements for successful identification of correlates of protection in secondary objective 1 are:

1. Sufficient sample size to observe enough participants diagnosed with incident HIV-1 infection during the primary follow-up period of 80 weeks postenrollment in the mAb arms

2. A result of significant beneficial overall mAb PE > 0%
3. Sufficiently frequent HIV-1 testing schedule and accurate HIV-1 diagnostics
4. Wide variability in the concentration and effector functions of the mAb over time and/or individuals, and the ability to measure these characteristics such that their timing relative to the timing of HIV-1 acquisition is estimated with adequately low measurement error
5. mAb marker sampling design that allows sufficiently accurate PK modeling of mAb characteristics over time

Note that the serum concentration mAb markers (secondary endpoints 2) are defined without reference to a particular HIV-1 Env sequence. The effector function markers (also secondary endpoints 2) are relative to specific HIV-1 Envs or panels of Envs, and thus may be linked to immunogenicity endpoints (and the antigen reagents for those endpoints) that would be used in future trials of candidate HIV-1 vaccines. Correlates of protection analyses directly assess how mAb PE depends on markers.

4.11.7.1 Sampling of mAb markers

Characteristics of the mAb or immune responses to the mAb are measured in participants assigned to the mAb treatment groups, and in a small number of participants assigned to the control group. The sampling design determining the set of participants for measuring the markers will be finalized after the primary analysis results. This sampling design will include measuring the markers in all mAb group primary endpoint cases with a minimal number of samples available prior to diagnosis of HIV-1 infection, and on a random sample of participants from each mAb group who complete follow-up to the Week 96 visit HIV-1 negative (mAb group control participants). The random sample of HIV-1 uninfected controls is chosen to create a common control:case ratio across participant strata defined by factors such as dose group, infusion adherence, and calendar period of enrollment. For participants assigned to the control group, a smaller number of cases and HIV-1 negative controls will be sampled for measurement of markers. The timing of marker measurements is as follows:

- mAb group and control group cases: visits every 4 weeks up until the time of HIV-1 diagnosis and Day 61 (5 days post second infusion) if before diagnosis, plus the first positive visit and additional time-points post HIV-1 infection
- mAb group and control group marker subset controls: visits every 4 weeks through Week 80 plus Day 61 and Weeks 88 and 96

The Day 5 post-second infusion visit is included because it occurs shortly after the end of the distributive phase of the mAb, which together with the samples drawn just before infusions (Week 0, 8, ..., 72), the samples drawn 4 weeks post-

infusions (Week 4, 12, ..., 76), and the Week 80, 88, and 96 samples 8–24 weeks post last infusion constitute the basis for modeling marker curves over time.

4.11.7.2 Overview of the analysis of a mAb marker as a correlate of protection

A correlates of protection statistical analysis plan will be finalized not using any information on case-control status of participants; this plan will contain details of the statistical analysis. We provide a brief summary here. For a given mAb recipient, let $S(t)$ be a marker characteristic at time t postenrollment in days, for example the time-concentration curve. The entire curve $S(t)$ cannot be known exactly given that the marker is measured at a grid of time-points. A PK model will be used to express $S(t)$ as a function of the measured marker readouts and error terms. One approach to the correlates of protection analysis will estimate the “prevention efficacy curve” $PE(S(t) = s)$ defined as

$$PE(S(t) = s) = [1 - (\text{hazard-mAb}(S(t) = s)) / (\text{hazard-control}(S(t) = s))] \times 100\%$$

where $\text{hazard-mAb}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to either mAb group with $S(t) = s$ and $\text{hazard-control}(S(t) = s)$ is the hazard rate of HIV-1 infection at time t for a participant assigned to the control group who would have had $S(t) = s$ had s/he been assigned to the same mAb group (thus $S(t)$ is a counterfactual random variable for control recipients). Similar parameters are used for assessing time-dependent correlates of protection in vaccine efficacy trials. A time-dependent parameter is used because interest centers on understanding how the current value of a mAb marker associates with the level of instantaneous PE given exposure with an HIV-1 virus at that time. The statistical analysis plan will describe the methods used to estimate $PE(s)$ over the range of values s of a mAb marker characteristic. In addition to estimation, hypothesis testing will be performed to assess whether a mAb marker modifies PE, ie, testing

$$H_0: PE(S(t) = s) = PE \text{ versus } H_1: PE(S(t) = s) \text{ varies in } s. \quad (1)$$

Rejecting H_0 in favor of H_1 supports the role of the marker in protection. The correlates of protection analysis pools over the two mAb groups, for the purpose of improving power both through a larger sample size and through greater inter-individual variability of the mAb markers. Given that the exact dates of infusions have a major impact on mAb markers $S(t)$ such as concentration over time (eg, notice the profound influence of missed infusions on $S(t)$ in [Figure 2-9](#)), the analysis accounts for the exact dates of infusions that are expected to show considerable heterogeneity across trial participants.

4.11.7.3 A time-window approach to assessing mAb correlates of protection

To explain the concept of this approach, first suppose all participants received all scheduled infusions and rigidly followed the visit schedule. Then this approach compares HIV-1 incidence during the first 4 weeks of the infusion intervals (ie, weeks 1-4, 9-12, 17-20, ..., 73-76) to HIV-1 incidence during the second 4 weeks

of the infusion intervals (ie, weeks 5-8, 13-16, 21-24, ..., 77-80), aggregating over the ten 8-week infusion intervals. Because the mAb has much higher concentration during the first halves of the infusion intervals compared to the second halves (eg, demonstrated in [Figure 2-9](#)), detection of higher HIV-1 incidence in the second halves of visit windows would imply that higher concentrations are associated with a lower rate of HIV-1 infection.

However, because of missed infusions and the heterogeneity among participants of infusion dates (which is allowable as specified by broad visit windows), a better approach accounts for the set of exact infusion dates of each participant. As such, our approach to implementing the time-window approach compares the mean time between the last infusion and infection for VRC01 group cases, with the mean of the participant-specific weighted average time between infusions of VRC01 group control participants, where the weights allow for changing HIV-1 incidence over time. The analysis stratifies by the 10 mg/kg and 30 mg/kg dose groups and aggregates estimates over these two dose groups. In addition, an important element of the analysis uses predictions of the HIV-1 infection times for all VRC01 group cases. Models for these predictions are built using information on HIV-1 diagnostic tests, intra-host diversity of HIV-1 sequences, HIV-1 viral loads, and perhaps other factors. Initial research to build predictors of HIV-1 infection time based on HIV-1 sequence information has been conducted using validation data sets of acutely HIV-1 infected individuals [127].

A related approach to assessing correlates of protection integrates a pharmacokinetic model of the serum concentration of VRC01 over time, comparing the mean VRC01 concentration at the time of HIV infection for VRC01 group cases with the mean of participant-specific weighted average VRC01 concentrations over follow-up time. The participant-specific average VRC01 concentration over follow-up time is intended to reflect the expected concentration at the time of a random HIV exposure, with weighting used as above to allow for changing HIV-1 incidence over time. Details of these statistical methods will be provided in the statistical analysis plan.

4.11.7.4 mAb markers

For effector function markers measured based on a sample from a mAb recipient, the markers are measured to each of a panel of HIV-1 Envelope proteins. The most relevant HIV-1 Env panel represents the VRC01 antibody footprint diversity of viruses exposing trial participants. For example, relevant for the study population that is mostly exposed to subtype C HIV-1, [Figure 4-7](#) shows a logo plot of the VRC01 antibody footprint motifs comprising 35 amino acid sites [19] based on 444 subtype C sub-Saharan African sequences deposited in the Los Alamos National Laboratory (LANL) sequence database between 2006 and 2014.

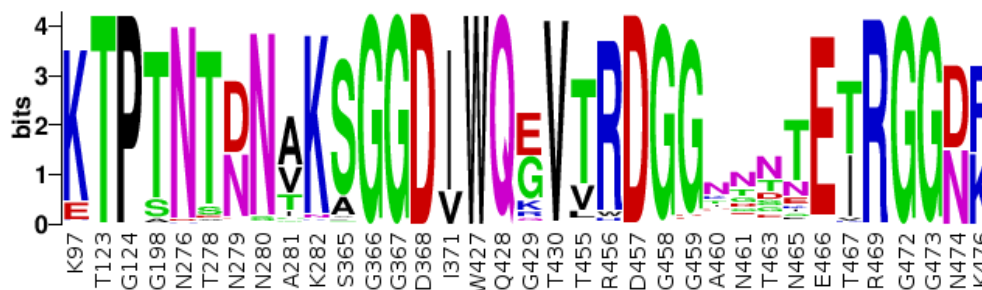


Figure 4-7 Logo plot of the VRC01 antibody footprints that occur in 444 subtype C sub-Saharan African sequences deposited in the LANL sequence database between 2006 and 2014

During the conduct of the trial the research team will determine a minimal set of Envs constituting a panel capturing most of the VRC01 mAb footprint diversity of exposing viruses. One effector function marker of interest for assessing as a correlate of protection is the weighted area under the magnitude-breadth neutralization curve of the mAb footprint Env panel, where the weighting is by the estimated prevalence of mAb footprints in HIV-1s circulating at the trial sites during the trial.

For mAb group participants with a primary study endpoint (breakthrough HIV-1 infection during the first 80 weeks), an important marker is the level at which his/her pre-infection sample at the time of HIV-1 acquisition neutralizes his/her particular breakthrough virus. (This analysis requires modeling the marker at the time of HIV-1 acquisition based on the available grid of marker measurements.) A result where sera from infected participants generally fail to neutralize their founding viruses would support neutralization as a correlate of protection. This analysis is repeated for other effector functions as a way to discriminate which effector functions are or are not correlates of protection, and to rank the effector functions by their contribution to explaining the level of protection.

4.11.7.5 Statistical power for assessing a mAb marker as a correlate of protection

The marker $S(t)$ must vary within mAb recipients over time and/or among mAb recipients in order to detect a correlate of protection, with more variability in one or both components providing greater statistical power to detect a correlate of protection via testing the null hypothesis of equation/panel (1) above. In essence, to detect correlates of protection it is necessary that a large fraction of person-years at risk are in high protection zones and a large fraction of person-years at risk are in low protection zones. (A “high protection zone” is a period of time during which a mAb recipient has high levels of a marker and high levels of efficacy.) Data from VRC 601, VRC 602, and HVTN 104 show wide variability in the mAb concentration over time, and more limited variability among mAb recipients. HVTN 104 will provide more data on these two aspects of marker variability. The limited among-mAb recipient variability motivates the study design that randomly assigns participants to 2 different mAb doses in order to create inter-individual variability.

Achieving adequate power to detect correlates of protection requires that the HIV-1 diagnostic testing is more frequent than the infusion schedule. This is why diagnostic visits every 4 weeks are advantageous given infusions every 8 weeks, and procedures may be determined and applied to test for HIV-1 infection more frequently than every 4 weeks. The data from all of the employed diagnostic testing kits is incorporated into the modeling of $S(t)$ and of HIV-1 infection times, and is integrated into the statistical analysis for estimation and testing of $PE(S(t) = s)$. Lastly, achieving adequate power to detect correlates of protection requires studying markers that can be measured with a high ratio of potentially protection relevant variability versus protection irrelevant variability, where the latter variability could stem from technical measurement error of the assay or to error in estimation of the timing of infection. Because of this fact the trial design relies on parallel assay studies to qualify marker variables for the analysis and relies on development and characterization of models for $S(t)$ over continuous time t .

We provide one power calculation for assessing a trichotomous marker $S(t)$, the concentration of the mAb at time t post enrolment, as a correlate of protection, which divides the pooled mAb group at a given time t by two thresholds of marker response [$S(t) = 0$ indicates Low, $S(t) = 1$ indicates Medium, and $S(t) = 2$ indicates High for some pre-set definitions of Low, Medium, High]. Thus at any given time t after entry, $S(t)$ divides the pooled mAb group into three subgroups. In our illustration we take “0” to be a VRC01 serum concentration ≤ 50 mcg/mL, “2” to be a VRC01 serum concentration > 10 mcg/mL, and “1” to be an intermediate serum concentration.

Based on [Figure 2-4](#), we conduct a power calculation indexed by the percentage of person-years at-risk of mAb recipients that are in the (Low, Medium, High) zones, and indexed by the level of PE within each of these zones. As indicated in the figure, we expect that about (50%, 40%, and 10%) of the PYRs at risk in the 10 mg/kg mAb group are in the (Low, Medium, and High) regions whereas about (10%, 40%, and 50%) of the PYRs at risk in the 30 mg/kg mAb group are in the (Low, Medium, and High) regions. We consider power calculations pooling data across both mAb groups, assuming 30 mAb HIV-1–infected cases with data and 150 mAb group HIV-1–uninfected controls with data, assuming the design alternatives $PE_{10} = PE_{30} = 60\%$ approximating the numbers displayed in [Table 4-3](#). The detailed mathematical assumptions of these power calculations will be provided in the statistical analysis plan.

[Figure 4-8](#) shows power curves for the scenario that (30%, 40%, 30%) of PYRs at risk are in the (Low, Medium, High) zones (which we approximately expect to occur based on [Figure 2-4](#)) and $PE_{10} = PE_{30} = (15\%, 60\%, 85\%)$ in these zones. The power curves also account for noise in the measurement of $S(t)$ via a parameter ρ that equals the proportion of the inter-individual marker variability that is potentially protection relevant. The results show that the noise level majorly affects power, underscoring that only assays meeting qualification criteria will be studied as correlates. The parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values of $S(t)$ are

needed. For the scenario that this extra variability reduces ρ to 0.7, there is about 80% power to detect a correlate of protection (with effect size 15%, 60%, 85% efficacy) at the selected trial sample size. Note that the parameter ρ also reflects noise due to uncertainty in the exact times t of HIV-1 acquisition at which values $S(t)$ are needed. A more extensive set of power calculations will be conducted based on HVTN 104 study data.

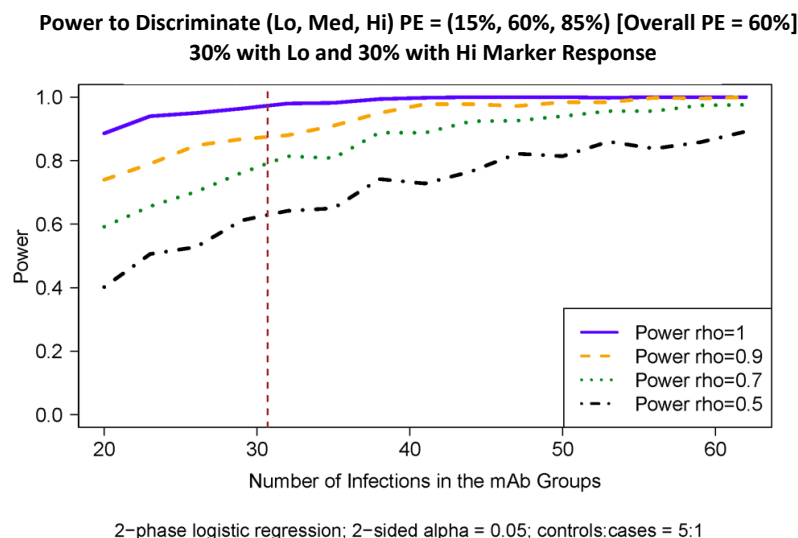
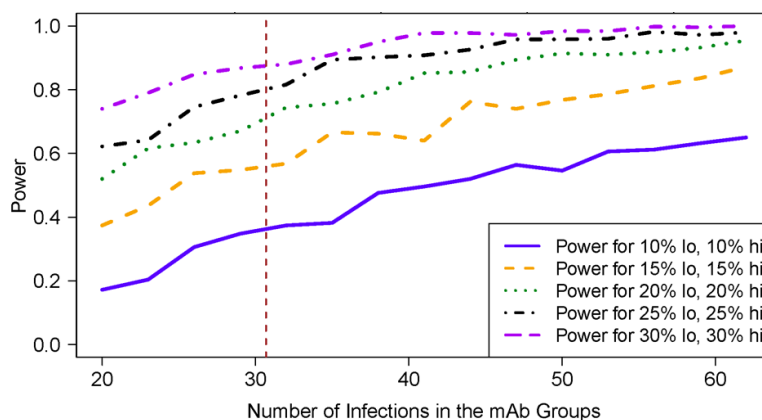


Figure 4-8 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE = 15%, 60%, 85%, respectively, for a marker with assay noise parameter ρ = 1 (perfect marker), 0.9, 0.7, and 0.5 and percentages of person-years at risk in the (Low, Medium, High) marker regions set at (30%, 40%, 30%). The calculations at 1900 total participants assume 30 mAb group HIV-1–infected cases and 150 mAb group HIV-1–uninfected controls with data on $S(t)$ and pool over both mAb groups. The dashed vertical line represents the sample size of the study.

Figure 4-9 shows the same power analysis as Figure 4-8, fixing ρ = 0.9 (indicating a qualifying assay) and varying the percentage of PYRs at risk that are in the (Low, Medium, High) zones. The results show that power increases sharply with the percentage of mAb recipients that are in the Low and High regions, demonstrating the principle that variability in the marker is a strong determinant of power to detect a correlate of protection.

Power to Discriminate (Lo, Med, Hi) PE = (15%, 60%, 85%) [Overall PE = 60%; rho = 0.9]

2-phase logistic regression; 2-sided alpha = 0.05; controls:cases = 5:1

Figure 4-9 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups $S(t)$ = Low, $S(t)$ = Medium, and $S(t)$ = High at level PE = 15%, 60%, 85%, respectively, for a marker with assay noise parameter $\rho = 0.9$ and percentages of person-years at risk in the Low and High marker regions varied from 10%, 15%, 20%, 25%, 30%. The calculations at 1900 total participants assume 30 mAb group HIV-1-infected cases and 150 mAb group HIV-1-uninfected controls with data on $S(t)$ and pool over both mAb groups.

4.11.7.6 Genotypic and phenotypic sieve analysis

Genotypic sieve analysis analyzes sequences of breakthrough HIV-1 infecting viruses from the earliest available postinfection sample and seeks to identify amino acid “signatures” that differentiate breakthrough sequences in the mAb groups versus the control group, in terms of differential PE against HIV-1s according to some genotypic characteristics. For example, the genotypic sieve analysis assesses differential PE against different genotypes of HIV-1 with genotype defined by:

- Number of mismatches to the VRC01 mAb footprint of the subtype C consensus sequence (subtype selected to match the circulating HIV-1s)
- Number of known mAb neutralization escape mutations in the mAb footprint
- Number of known mAb effector function escape mutations in the mAb footprint for non-neutralization effector functions such as ADCC, virion capture, and phagocytosis
- Number of potential N-linked glycosylation (PNG) sites within a given radius of the mAb footprint
- Length of variable loops in proximity to the mAb footprint

To illustrate the utility of genotypic sieve analysis, we consider a hypothetical result that would support that the mAb protects via specific neutralization targeting of the mAb’s epitope. In this illustration, the HIV-1 genotype is defined by four ordered genotypes according to whether there are 0, 1, 2, or >2 neutralization escape mutations in the VRC01 mAb antibody footprint. The hypothetical result would be an estimated PE of 95% against HIV-1s with zero

escape mutations and a PE of 0% against HIV-1s with >2 neutralization escape mutations, and intermediate and monotone decreasing level of estimated PE against HIV-1 with one mutation and two mutations, respectively.

A second type of sieve analysis, phenotypic sieve analysis, compares breakthrough viruses between the mAb versus control groups using an immunological assay. Specifically, data from an “effector function checkerboard” is filled out, with the rows representing serum samples from a random sample of mAb recipients HIV-1 uninfected at the time of sampling, and the columns representing HIV-1 Env VRC01 footprint targets created from the breakthrough viruses. The phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to mAb recipient sera between the mAb and control treatment groups. A second version of the phenotypic sieve analysis compares the sensitivity of the breakthrough viruses to the VRC01 mAb between the treatment groups; this latter analysis is simpler, based on a single column of data instead of a matrix, because it does not use mAb recipient sera. For an example of the second type of phenotypic sieve analysis, the TZM-bl neutralization assay could be performed on all control breakthrough HIV-1s versus VRC01 and on all mAb group breakthrough HIV-1s (pooled over the two mAb groups) versus VRC01, and a Wilcoxon rank sum test applied to assess a difference. Reduced TZM-bl neutralization sensitivity of the mAb breakthrough group viruses would support that neutralization had a role in protection and that the TZM-bl assay was able to detect this role, and would support using the TZM-bl assay as a tool for evaluating future candidate HIV-1 vaccines. The HVTN has previously conducted neutralization sieve analysis [128]. Figure 4-10 illustrates a genotypic and phenotypic sieve analysis.

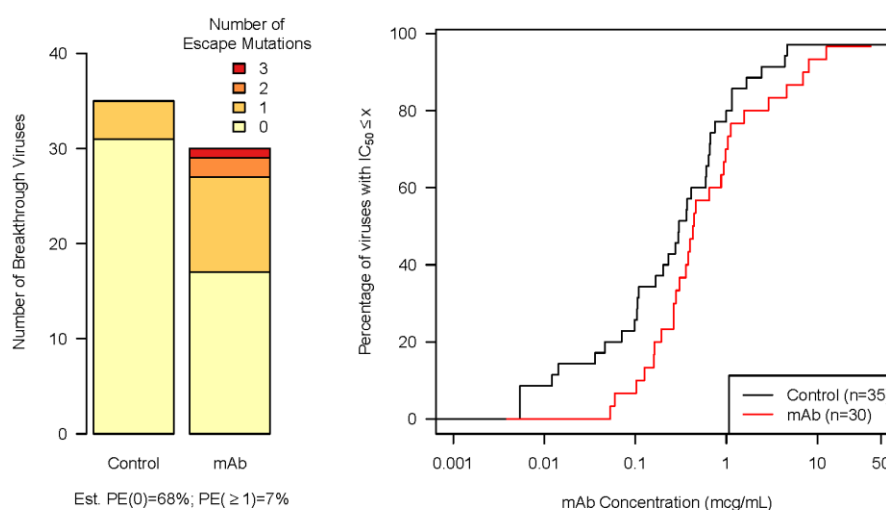


Figure 4-10 Illustration of genotypic (left panel) and phenotypic (right panel) sieve analysis, where the left panel shows the distribution of the number of known neutralization escape mutations in breakthrough control and mAb group HIV-1 sequences, and the right panel shows the percentage of the panel of breakthrough HIV-1s that are neutralized at level 50% (IC₅₀) by the given concentration of the VRC01 mAb.

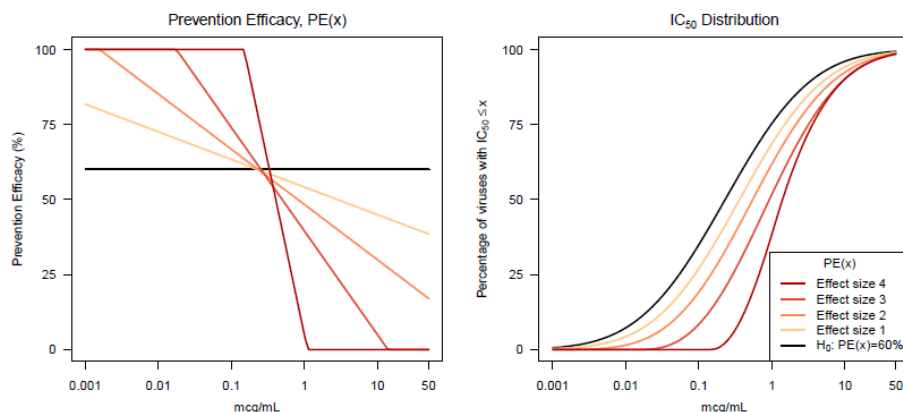
Another phenotypic sieve analysis focuses on mAb group cases, and measures different effector functions of closest-to-infection participant serum samples or of the VRC01 mAb against the participant-matched breakthrough HIV-1s. The effector functions that tend to have low readouts against participant-matched breakthrough viruses compared to against the panel of control group HIV-1s or compared to an historic panel of HIV-1s are implicated as potential correlates of protection.

In addition, an important sieve analysis will assess PE against HIV-1s that are sensitive to neutralization by VRC01 as measured using the first post-infection sample (sensitive is defined by positive neutralization based on IC_{50} or IC_{80}). This PE parameter measuring prevention efficacy against neutralization sensitive HIV-1s is estimated (with confidence intervals and p-values) in the same way as genotype-specific PE described above. In addition, the same hypothesis testing procedure for detecting differential PE by two HIV-1 genotypes is applied for assessing differential PE by neutralization sensitive versus resistant HIV-1. Moreover, this sieve analysis of sensitive versus resist HIV-1 is also conducted with sensitive/resistant defined by positive/negative response of other assays besides neutralization (eg, ADCC, ADCP).

4.11.7.7 Illustration of power to detect a phenotypic sieve effect

We conduct power calculations based on TZM-bl neutralization IC_{50} values (in mcg/mL) of VRC07 (a close cousin of VRC01) to approximately 100 viruses representing global HIV-1 diversity (data provided by Mark Louder, Robert Bailer, and John Mascola from the VRC). From the control group we sample 35 HIV-1 infections with IC_{50} from the VRC07 data set, and from the pooled mAb group we sample 30 HIV-1 infections with IC_{50} values bias sampled based on IC_{50} -dependent PE, with $PE(x)$ the probability an infected control recipient would be infected had she received the mAb with IC_{50} value of x to the exposing virus.

Figure 4-11 shows power for comparing the VRC01 IC_{50} distribution of the pooled mAb group HIV-1s versus the control group HIV-1s, based on a two-sample Wilcoxon rank sum test. The effect size indexing a difference between the two groups is equivalently expressed in terms of the $PE(x)$ function (where a horizontal line indicates the null hypothesis of no difference) or in terms of a different cumulative distribution function of the IC_{50} in the two groups. Four correlates effect sizes are considered, ranging from the weakest (Effect Size 1) to the strongest (Effect Size 4). The results show that there is moderate power to detect Effect Size 3 phenotypic sieve effects (second steepest curve in Figure 4-11, power = 0.793).



Power of Wilcoxon test (2-sided 0.05 level test)				
PE(x)	Number of control cases			
	25	30	35	40
Effect size 4	93.9	97.1	98.6	99.4
Effect size 3	65.1	72.8	79.3	85.4
Effect size 2	27.2	31.0	36.9	41.1
Effect size 1	10.2	11.1	12.5	13.8
H ₀ : PE(x)=60%	4.7	4.9	4.9	5.0

Figure 4-11 Power calculations for comparing IC_{50} distributions between mAb group breakthrough HIV-1s and control group breakthrough HIV-1s, with difference equivalently expressed in terms of the $PE(x)$ curve or the cumulative IC_{50} distribution functions, where in the right panel the black/highest curve represents the distribution for the control group breakthrough HIV-1s.

Effect Size 3 is biologically plausible based on the following argument. Under the design alternative of 60% PE we expect a transition between full protection against the most sensitive viruses and zero protection against the most resistant viruses. Table 4-7 shows the percentage of susceptible viruses that are completely blocked by the VRC01 antibody and the percentage of viruses that are completely resistant to the antibody for each of the four specified effect sizes $PE(x)$ in Figure 4-11. For example, for Effect Size 3, the most susceptible 11.6% of viruses are completely blocked ($PE = 100\%$) while the most resistant 2.8% of viruses are completely resistant ($PE = 0\%$) and there is a gradient of protection for the 85.6% of intermediate viruses between the two poles (Table 4-7). The wide range of neutralization (and Fc effector function) sensitivities of HIV-1s suggests that this range of prevention efficacies is plausible. For this effect size there is 79.3% power to detect a phenotypic sieve effect and hence a correlate of protection.

Table 4-7 Percentages of HIV-1s fully susceptible to VRC01 (PE = 100%) and fully resistant to VRC01 (PE = 0%) for the four different effect sizes studied in [Figure 4-11](#)

PE(x) Effect Size in Figure 1-16	<i>Susceptible</i> [PE = 100%]	<i>Resistant</i> [PE = 0%]
Effect Size 4	41.9%	23.3%
Effect Size 3	11.6%	2.8%
Effect Size 2	1.0%	<0.1%
Effect Size 1	<0.1%	<0.1%
Null Hypothesis	NA	NA

The sieve analyses will be done including all MITT infected participants, as well as only including mAb group infected participants who received an infusion at the beginning of the 8-weekly interval during which HIV-1 infection was diagnosed.

5 Selection and withdrawal of participants

Participants will be healthy, HIV-uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on information available at the time of enrollment, including results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

Investigators should always use good clinical judgment in considering a volunteer's overall fitness for trial participation. Some volunteers may not be appropriate for enrollment even if they meet all inclusion/exclusion criteria. Medical, psychiatric, occupational, or other conditions may make evaluation of safety and/or serum mAb concentration and efficacy difficult, and some volunteers may be poor candidates for retention.

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections [5.1](#) and [5.2](#).

5.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 40 years
2. **Access to a participating CRS** and willingness to be followed for the planned duration of the study
3. Ability and willingness to provide **informed consent**
4. **Assessment of understanding:** volunteer demonstrates understanding of this study and completes a questionnaire prior to first infusion with verbal demonstration of understanding of all questionnaire items answered incorrectly
5. **Agrees not to enroll in another study** of an investigational research agent for the duration of the participant's trial participation
6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

7. Willingness to receive **HIV test results**

8. Willingness to **discuss HIV infection risks** and amenable to HIV risk reduction counseling
9. **Persons born Female (assigned female sex at birth) and identifying as female**, who, in the 6 months prior to randomization, has had vaginal and/or anal intercourse with a male partner

Volunteers who have been in a mutually monogamous relationship with an HIV-1 seronegative partner for > 1 year are excluded.

Laboratory Inclusion Values

Hematology

10. **Hemoglobin** (Hgb) ≥ 10.5 g/dL
11. **Platelets** $\geq 100,000$ cells/mm³

Chemistry

12. **ALT** < 2.5 times the institutional upper limit of normal and creatinine ≤ 1.25 times the institutional upper limit of normal

Virology

13. **HIV uninfected, as defined in the SSP, within 30 days prior to enrollment**

Urine

14. **Negative, trace, or 1+ (30 g/L for semi-quantitative) urine protein by dipstick**

Reproductive Status

15. **Volunteers capable of becoming pregnant:** negative serum or urine beta human chorionic gonadotropin (β -HCG) pregnancy test performed at the screening visit and prior to infusion on the day of initial infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing.
16. **Reproductive status:** A volunteer who is capable of becoming pregnant must agree to consistently use effective contraception (see [Appendix B](#) and SSP) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit.
17. **Volunteers capable of becoming pregnant must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

5.2 Exclusion criteria

General

1. **Investigational research agents** received within 30 days before first infusion
2. **Body mass index (BMI)** ≥ 40
3. **Pregnant or breastfeeding**
4. **Any reactive, indeterminate, or positive HIV test**, even if subsequent testing indicates that the individual is not HIV infected, except as permitted by the HVTN 703/HPTN 081 PSRT

Vaccines

5. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 703/HPTN 081 PSRT will determine eligibility on a case-by-case basis.

Immune System

6. **Serious adverse reactions to VRC01 formulation components such as sodium citrate, sodium chloride, and L-arginine hydrochloride**, including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.
7. **Autoimmune disease**, including Type I diabetes mellitus (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require consistent immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate reactogenicity and AE assessments)
8. **Immunodeficiency syndrome**

Clinically significant medical conditions

9. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health. A clinically significant condition or process includes but is not limited to:
 - Any contraindication to repeated infusions or blood draws, including inability to establish venous access;
 - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period; or

- A condition or process for which signs or symptoms could be confused with reactions to VRC01.
10. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence, assessment of safety or infusion reactions, or a volunteer's ability to give informed consent
 11. **Psychiatric condition that precludes compliance with the protocol.**
Specifically excluded are persons with psychoses within the past 3 years, ongoing risk for suicide, or history of suicide attempt or gesture within the past 3 years.
 12. **Asthma**, other than mild, well-controlled asthma
 13. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
 14. **Malignancy** (Not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure. or who is unlikely to experience recurrence of malignancy during the period of the study)
 15. **Seizure disorder:** History of seizure(s) within past three years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.
 16. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema
 17. History of **receiving transplantation of life-saving organs or tissue** (includes heart, kidney, pancreas, lungs, liver, and intestines)
 18. **Known hepatic or renal dysfunction**

5.3 Participant departure from infusion schedule or withdrawal

This section concerns an individual participant's departure from the infusion schedule. Pause rules for the trial as a whole are described in Section 10.3.

5.3.1 Delaying infusions for a participant

Under certain circumstances, a participant's scheduled infusion will be delayed. The factors to be considered in such a decision include but are not limited to the following:

- Prior to infusion, abnormal vital signs or clinical symptoms that may mask assessment of a study product reaction

- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delay or withdrawal from the infusion schedule. The investigator may consult with the HVTN 703/HPTN 081 PSRT.
- Pregnancy: for participants who become pregnant infusions will be stopped. If the participant is no longer pregnant (as demonstrated by a negative urine or serum pregnancy test) and wants to continue with infusions, the HVTN 703/HPTN 081 PSRT will be consulted to determine whether the participant may resume infusions or whether infusions should be permanently discontinued.

5.3.2 Participant departure from infusion schedule

Every effort should be made to follow the infusion schedule per the protocol. If a participant misses an infusion and the visit window period for the infusion has passed, then sites may consult the SSP.

5.3.3 Discontinuing infusions for a participant

Under certain circumstances, an individual participant's infusions will be permanently discontinued. Specific events that will result in stopping a participant's infusion schedule include:

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of infusions may be granted with the unanimous consent of the HVTN 703/HPTN 081 PSRT);
- Clinically significant condition (ie, a condition that affects the immune system or for which continued infusions and/or blood draws may pose additional risk), including but not limited to the following:
 - Any grade 4 local or systemic reactogenicity symptom or AE that is subsequently considered to be related to study product;
 - An SAE that is subsequently considered to be related to study product;
 - Any grade 3 clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to study product;
 - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product;
 - Clinically significant hypersensitivity reaction including but not limited to type 1 hypersensitivity reaction and/or serum sickness associated with study product. Consultation with the HVTN 703/HPTN 081 PSRT is required prior to subsequent infusion following any hypersensitivity reaction associated with study product; or

- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).

Infusions will be permanently discontinued for a participant diagnosed with HIV infection or with 2 reactive HIV tests, even if subsequent testing indicates that the participant is not HIV infected.

Participants for whom infusions are discontinued for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in Schedule 4 follow-up visits and protocol-specified procedures (see [Appendix I](#) and [Appendix M](#)), unless medically contraindicated.

5.3.4 Participant termination from the study

Under certain circumstances, an individual participant may be terminated from participation in this study. Specific events that will result in early termination include:

- Participant refuses further participation
- Participant relocates and remote follow-up or transfer to another CRS is not possible
- CRS determines that the participant is lost to follow-up
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff)
- Any condition where termination from the study is required by applicable regulations.

6 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in [Table 1-1](#). See the IBs for further information about study products.

6.1 Study product regimen

The schedule of study product administrations is shown in [Section 1](#) and additional information is given below.

Group 1 [Note – participants randomized under Version 1.0 were enrolled in this same treatment but under the assignment “Treatment 4(T4)”]

Treatment 1 (T1): VRC-HIVMAB060-00-AB 10 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to prepare a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 2 [Note – participants randomized under Version 1.0 were enrolled in this same treatment but under the assignment “Treatment 5(T5)”]

Treatment 2 (T2): VRC-HIVMAB060-00-AB 30 mg/kg in sufficient Sodium Chloride for Injection USP, 0.9% to prepare a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

Group 3 [Note – participants randomized under Version 1.0 were enrolled in this same treatment (control) but under the assignment “Control 6(C6)”]

Control 3 (C3): Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) to be prepared as a final total volume of 150 mL IV at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, and 72.

For all participants originally enrolled under Version 1.0, a new prescription must be written and sent to the pharmacy once the participant has consented under Version 2.0 with the appropriate 4-digit CODE written on the prescription as well as a way for the pharmacist to verify that the participant has consented under Version 2.

6.2 Study product formulation

VRC-HIVMAB060-00-AB [VRC01, Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB]

VRC01 will be provided as a sterile clear, colorless to yellow isotonic solution, essentially free of visible particles; some white, opaque particles may be present. Each vial contains 100 mg / mL of VRC-HIVMAB060-00-AB in formulation buffer. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. Vials are intended for single use only and do NOT contain a preservative. The product should be stored frozen -35°C to -15°C with excursions permitted between -45°C and -10°C. The study products are described in further detail in the IB.

VRC01 is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C (36°F to 46°F).

Prior to preparation, vials containing VRC01 must be removed from the freezer and thawed for a minimum of 1 hour at controlled room temperature (maximum 27°C). Following this 1 hour thaw, the unopened vials of VRC01 may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 4 weeks at 2°C to 8°C. Product may NOT be thawed or stored in direct sunlight. Once thawed, product may NOT be refrozen.

Prior to preparation, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS.

If particles are observed, return the vials to 2°C to 8°C storage.

If the particles re-dissolve within the maximum storage time of up to 4 weeks at 2°C to 8°C, the vials may be used for product preparation. Refrigerated product in the vial must be equilibrated at controlled room temperature (maximum 27°C) for a minimum of 30 minutes before preparation and must be used within 8 hours of removal from the refrigerator.

If particles continue to be observed after 4 weeks at 2°C to 8°C, do not use the vial product for IV bag preparation. These vials must be quarantined until they are returned to the NIAID Clinical Research Products Management Center (CRPMC) or to the manufacturer upon request of the CRPMC or destroyed if directed by the CRPMC.

Control for VRC01 [Sodium Chloride for Injection USP, 0.9%]

Sodium Chloride for Injection USP, 0.9% will be used as the Control for VRC01. It must be stored as directed by the manufacturer. For sites who do not have access to Sodium Chloride for Injection USP, 0.9%, the Sodium Chloride for Injection, 0.9% that they use must meet the following criteria: a sterile solution of Sodium Chloride in Water for Injection which contains no antimicrobial agents. It is nonpyrogenic and is intended for intravenous administration.

6.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription **MUST** contain the participant's weight based upon the participant's weight at the most recent visit where weight was measured (this includes screening) and randomization code (this may NOT be communicated verbally). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 38 General Chapter Physical Tests / <797> Pharmaceutical Compounding - Sterile, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

6.3.1 VRC-HIVMAB060-00-AB (10mg/kg IV) - (Group 1)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($10 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for up to 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. **DO NOT SHAKE VIALS**. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will then add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as "VRC01 or Control in Normal Saline Total Volume = 150 mL". The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a **DO NOT INFUSE** after date and time as follows:

- 24 hours if stored at 2°C to 8°C

- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than the timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.2 VRC-HIVMAB060-00-AB (30mg/kg IV) - (Group 2)

To prepare an IV infusion, the pharmacist will calculate the dose [total milligrams needed ($30 \text{ mg/kg} \times \text{participant's weight in kg}$)] and remove the total number of vials needed as well as a 100 mL IV bag of Sodium Chloride for Injection USP, 0.9% from storage. If the product has been stored at 2°C to 8°C, the vials should be equilibrated to room temperature for 30 minutes and may be held at room temperature (not to exceed 27°C) for up to 8 hours prior to product preparation. The pharmacist will also calculate the additional amount of Sodium Chloride for Injection USP, 0.9% needed to prepare a final total volume of 150 mL and remove this from storage.

Prior to preparation, the pharmacist should gently swirl the vials containing VRC01 and then inspect for particles. DO NOT SHAKE VIALS. If visible particles are present, the product will not be used (see Section 6.2 for more information). The pharmacist, using aseptic technique, will add the appropriate amount of Sodium Chloride for Injection USP, 0.9% to the 100 mL IV bag of Sodium Chloride for Injection USP, 0.9%. The pharmacist, still using aseptic technique will then add the appropriate volume of VRC01 to that same bag for a final total volume of 150 mL. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

Any empty vials, unused portion of entered vials, or unused IV solution that contains study product should be discarded in a biohazard containment bag and incinerated or autoclaved in accordance with institutional or pharmacy policy.

6.3.3 Control for VRC01 (Groups 3)

To prepare an IV infusion, the pharmacist, using aseptic technique, will add 50 mL of Sodium Chloride for Injection USP, 0.9% to a 100 mL bag of Sodium Chloride for Injection USP, 0.9%. The IV bag will be labeled as “VRC01 or Control in Normal Saline Total Volume = 150 mL”. The weight used for calculating the dose should be written on the label. A bag cover will be placed over the bag and should not be removed by the clinic staff. The IV bag will be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if stored at controlled room temperature (not to exceed 30°C)

Product may NOT be stored in direct sunlight.

Note: Site pharmacists must follow their institutional policies for expiration dates (ie, DO NOT INFUSE after date and time), if shorter than timeframes above.

6.4 Administration

VRC01 or Control (Intravenously)

Prior to infusion, if the VRC01 or Control IV bag has been stored at 2°C to 8°C, the bag must be equilibrated to room temperature (maximum of 30°C) for 30 minutes or longer and may be held for up to 8 hours, including equilibration time and completion of product administration. (NOTE: This 8 hour period may NOT exceed the DO NOT INFUSE after date and time on the IV bag label.)

The IV bag prepared by the pharmacy will include the weight that was used for preparation of the IV bag (VRC01 or Control). The clinician responsible for administration will check the bag label and confirm that the participant identifier is correct and that the weight on the bag label is within 10% of the participant's current actual weight (see Section 6.3 for more information).

An in-line filter infusion set must be used for IV administration (see SSP for specifications and additional details).

The entire contents of the investigational study product solution will typically be administered IV over about 15 to 60 minutes using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as participant tolerance.

6.5 Acquisition of study products

VRC-HIVMAB060-00-AB is provided by the VRC/DAIDS/NIAID.

Control for VRC01 (Sodium Chloride for Injection USP, 0.9%) will not be provided through the protocol and must be obtained by the site.

Once a CRS is protocol registered, the pharmacist can obtain study products from the CRPMC by following the ordering procedures given in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

6.6 Pharmacy records

The CRS pharmacist is required to maintain complete records of all study products. The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

6.7 Final disposition of study products

All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the CRPMC. The procedures and relevant form are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

7 Clinical procedures

The schedules of clinical procedures are shown in [Appendix J](#) through [Appendix M](#).

7.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The informed consent form documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in this study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures.

The informed consent process continues throughout the study. Key study concepts should be reviewed periodically with the participant and the review should be documented. At each study visit, CRS staff should consider reviewing the procedures and requirements for that visit and for the remaining visits. Additionally, if any new information is learned that might affect the participants' decisions to stay in the trial, this information will be shared with trial participants. If necessary, participants will be asked to sign revised informed consent forms.

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to their Institutional Review Board/Ethics Committee (IRB/EC) and any applicable Regulatory Entity (RE) for human subjects protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is “Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs [informed consent forms] prior to implementation at a site.” CRSs are responsible for knowing the requirements of their applicable REs.

7.1.1 Screening consent form

Without a general screening consent, screening for a specific study cannot take place until the site receives protocol registration from the DAIDS RSC Protocol Registration Office.

Some CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV prevention trial. In this way, CRS staff can continually screen potential

participants and, when needed, proceed quickly to obtain protocol-specific enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time period specified in the eligibility criteria.

7.1.2 Protocol-specific consent forms

The protocol-specific consent forms describe the study products to be used and all aspects of protocol participation, including screening and enrollment procedures. A sample protocol-specific consent form for the main study is located in [Appendix A](#). A separate sample consent form for other uses of specimens is located in [Appendix C](#).

Each CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in [Appendix A](#) and [Appendix C](#). The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC, and any applicable RE
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their site-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the level of understandability.

The sample informed consent form includes instructions throughout the document for developing specific content.

Sites should follow the instructions in the Protocol-specific Official Memo distributed along with this protocol regarding when they may begin using their site-specific protocol consent forms.

Regarding protocol registration, sites should follow procedures outlined in the current version of the DAIDS Protocol Registration Manual.

7.1.3 Assessment of Understanding

Study staff are responsible for ensuring that participants fully understand the study before enrolling them. This process involves reviewing the informed consent form with the participant, allowing time for the participant to reflect on the procedures and issues presented, and answering all questions completely.

An Assessment of Understanding is used to document the participant's understanding of key concepts in this clinical trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary. Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

IRB/EC and any applicable RE may require that a participant has signed either a screening or protocol-specific consent document prior to administering the Assessment of Understanding. The consent process (including the use of the Assessment of Understanding) should be explained thoroughly to the IRB/EC and any applicable RE, whose recommendations should be followed.

7.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before infusion on Day 0. All inclusion and exclusion criteria must be assessed within 56 days before enrollment, with the exception of HIV testing, which must be performed within 30 days before enrollment (see Section 5.1), unless otherwise specified in the eligibility criteria (or below in this section).

After the appropriate informed consent has been obtained and before enrollment, the following procedures are performed:

- Medical history, documented in the case history record;
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots;
- Laboratory tests as defined in the inclusion and exclusion criteria, including:
 - Screening HIV testing at local lab (see SSP)
 - CBC with differential
 - ALT
 - Creatinine
 - Urine dipstick
 - Urine or serum pregnancy test (volunteers capable of becoming pregnant); Persons who are not capable of becoming pregnant due to having

undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;

- Assessment of participant risk for HIV infection
- Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>);
- Counseling on HIV testing and risk reduction, performed in compliance with US CDC current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 7.5; and
- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in the study inclusion criteria and in [Appendix B](#). Discussion of pregnancy prevention includes advising a participant who reports no current sexual activity that could lead to pregnancy to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

7.2.1 Use of screening results from another HVTN or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this study, and the tests were conducted within the time periods specified in the eligibility criteria (see Section 5).

7.3 Enrollment and infusion visits

Enrollment is simultaneous with first infusion. The time interval between randomization and enrollment should not exceed 4 working days. The CRS requests the randomization assignment from the Web-based randomization system. Circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all infusion visits, the following procedures are performed before infusion:

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);

- Assessment of baseline reactogenicity parameters;
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- Assessment of concomitant medications (as described in Section 7.2);
- ALT;
- Creatinine;
- CBC with differential;
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Blood collection for HIV testing and sample storage.

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (see Sections 6.3 and 6.4).

Administration of an infusion and infusion-related procedures must be accomplished within 1 calendar day.

Immediately following the first infusion, the participant remains in the clinic for observation and initial reactogenicity assessment. See the SSP for details regarding infusion visit procedures and subsequent infusion observation and reactogenicity assessment procedures that CRSs must follow. The site will make arrangements to obtain a report of reactogenicity events from the participant after the 3-day reactogenicity period (as described in Section 7.10 and in the SSP).

The following procedures will be performed at all infusion visits. These procedures may be performed prior to, during, or following infusion:

- Administration of the participant questionnaire which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling);
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Risk reduction counseling (as described in Section 7.5);
- Pregnancy prevention assessment (as described in Section 7.2 and 7.6);

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled visits as specified in [Appendix J](#):

- Syphilis serology testing,
- Gonorrhea (GC)/chlamydia (CT) testing by urine or cervical/vaginal swab,
- Trichomonas by cervical/vaginal swab, and
- Urine dipstick (see Section [7.9](#)).

7.4 Post-infusion visits for HIV-uninfected study participants

The following procedures are performed at all post-infusion follow-up visits for HIV-uninfected study participants:

- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Blood collection for HIV testing and sample storage; and
- Ship samples to HVTN Central Laboratory for HIV diagnostic testing.

Additional procedures will be performed at scheduled follow-up visits as specified in [Appendix F](#) and [Appendix J](#):

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Administration of participant questionnaire, which may include acceptability, behavioral risk, study product belief, motivations, and social impact domains (must be done prior to risk reduction counseling)

- Risk reduction counseling (as described in Section 7.5);
- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Pregnancy prevention assessment (as described in Section 7.2 and 7.8);
- Assessment of new or unresolved AEs/intercurrent illnesses;
- Urine dipstick (see Section 7.9); and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.5 HIV counseling and testing

HIV counseling will be performed in compliance with the CDC's guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the protocol-specific HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection. In addition, study participants will be provided with HIV prevention supplies and referral to providers of PrEP per local and regional guidelines. Study investigators will ensure that participants have access to standards of care for HIV prevention in their local settings. As new data emerge and standards of care for HIV prevention evolve, both the content of risk reduction counseling and referrals for biomedical interventions will be updated to conform to current best practices for the population enrolled in this trial.

7.5.1 Study product–related seroreactivity

Human sera containing purified VRC01 at concentrations up to 1600 mcg/mL have been tested using a variety of commercially available HIV test kits without any indication of reactivity. For this reason, we do not anticipate that receipt of VRC01 will cause a reactive result on currently available HIV test kits, but this remains a theoretical possibility.

Because this possibility cannot be categorically eliminated, study staff will advise study participants to confine their HIV testing while in the study to that provided through the CRS. Staff will also inform study participants of the likelihood of routine HIV testing being offered or performed outside the study CRS at emergency rooms, clinics, and medical offices and will inform participants of their right to opt out of HIV testing outside the study site. CRS staff should

inform study participants if local and/or state/regional policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline HIV testing preemptively. CRS staff should also inform participants if positive HIV test results must be reported to local public health authorities. CRS staff should also inform participants of the need to maintain study blinding by getting HIV testing only at the study CRS. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV mAb clinical trial and should only be tested for HIV at the study CRS.

Study staff should also stress that the study product is completely cleared from the body within a few months, so even the theoretical risk of VRC01 causing a misleading HIV test result will disappear before their final scheduled clinic visit.

7.6 Follow-up visits for HIV-infected participants

The following procedures are performed at scheduled follow-up visits as specified in [Appendix G](#), [Appendix H](#), [Appendix K](#), and [Appendix L](#):

- Counseling on HIV testing and diagnosis;
- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- ART assessment;
- Assessment of concomitant medications (as described in Section [7.2](#));
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV transmission risk reduction counseling;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, viral load testing, VRC01 Ab levels, functional assays, viral isolation/sequencing, and sample storage (see [Appendix G](#) and [Appendix H](#));
- Blood collection for CD4+ T cell counts;

- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.7 Follow-up visits for participants who discontinue infusions for reasons other than HIV infection

Participants for whom infusions are discontinued for reasons other than HIV infection should be encouraged to continue in the study. For such participants, the following procedures are performed at approximately quarterly scheduled follow-up visits as specified in [Appendix I](#) and [Appendix M](#):

- Abbreviated physical exam including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints (see SSP for more detail);
- Risk reduction counseling (as described in Section [7.5](#));
- Assessment of concomitant medications (as described in Section [7.2](#));
- Assessment of any new or unresolved AEs/intercurrent illnesses;
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Behavioral risk assessment questionnaire;
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Blood collection for HIV testing, CBC/differential, ALT, creatinine, VRC01 Ab levels, functional assays, and sample storage (see [Appendix I](#) and [Appendix M](#));
- Urine dipstick (see Section [7.9](#));

- Urine or serum pregnancy test (for participants who are capable of becoming pregnant). Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin.

7.8 Contraception status

Contraception status is assessed and documented at screening and infusion visits for a participant who is capable of becoming pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. These participants should be reminded regularly of the importance of using contraception and should be referred to specific counseling, information, and advice as needed (see [Appendix B](#) for further detail.) This reminder should be documented in the participant's study record.

Infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation—must be documented in the participant's study record.

7.9 Urine testing

Urine dipstick testing may be performed in the clinic or the lab. The following analytes should be analyzed and recorded: specific gravity, protein, blood/hemoglobin, pH, urobilinogen, bilirubin, ketone, leucocyte esterase, nitrite, and glucose. The examination is performed on urine obtained by clean catch. Urine microscopy is required when the protein result is 1+, 2+, 3+, or 4+ (or semi-quantitative 30, 100, 300, or 2000 g/L) and/or the blood/hemoglobin result is trace, 1+, 2+, 3+, or 4+, but not required (unless otherwise clinically indicated) if the dipstick result is abnormal due to non-urinary bleeding.

If the dipstick performed for screening is transiently abnormal with an exclusionary result (eg, 2+ proteinuria), then repeat the dipstick and, if within the eligibility limits specified in the protocol, the participant may be enrolled (see SSP for further detail).

A follow-up urine test should be deferred if a participant is experiencing non-urinary bleeding (eg, menstruation), but should be performed as soon as possible. If a follow-up dipstick is abnormal due to non-urinary bleeding (eg, a participant's menstrual period), document in the comment section of the CRF and repeat the dipstick once the participant is no longer experiencing non-urinary bleeding. In this case, a urine microscopy is not required (see SSP for further

detail). If a follow-up dipstick is abnormal due to infection, document this issue in the participant's chart and provide appropriate treatment and/or referral.

7.10 Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after each infusion per the SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Corrected Version 2.1, dated July 2017, except as noted in Section [10.2.2](#).

The reactogenicity assessment period is 3 full days following each infusion. The site staff and the participant will be in contact after the 3-day reactogenicity period, or sooner if indicated. At that time, site staff will discuss reactogenicity events with the participant and record the relevant information on either the appropriate CRF(s) or participant chart note as source (for more details, see the SSP). Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. Participants are instructed to contact the clinic for events that arise during the period between infusion and the next scheduled visit. In general, a participant who self-reports any postinfusion reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity assessments include assessments of specific systemic and local signs and symptoms and IV infusion-related site reactions. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of infusion and 3 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse event log form.

For more detailed information and instructions on reactogenicity assessments, see the SSP.

7.10.1 Assessment of systemic and local signs and symptoms

Systemic signs and symptoms include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, and vomiting. Local symptoms include pain and/or tenderness proximal to the infusion site. The maximum severity reached for each symptom during the assessment period per the SSP is reported.

7.10.2 Assessment of infusion site

IV infusion-related site reactions may include redness/erythema and induration/swelling. The maximum horizontal and maximum vertical measurements for IV infusion-related site redness/erythema and induration/swelling are recorded.

All infusion site reactions are monitored until resolution. Areas greater than 25 cm² are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

7.11 Visit windows and missed visits

Visit windows are defined in the SSP. For a visit not performed within the window period, a Missed Visit form is completed.

If a participant misses a scheduled visit, CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. See the SSP for more details. If a participant missed an infusion visit or if infusions must be permanently discontinued, see Section 5.3.2 and Section 5.3.3 for resolution.

7.12 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, ALT, and Creatinine), pregnancy testing, social impact assessment, and HIV test.

7.13 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given during the pregnancy, but remaining visits and study procedures should be completed unless medically contraindicated. For participants who are no longer pregnant, see Section 5.3.1. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome.

8 HIV infection assessment and clinical response

8.1 HIV symptom assessment

At all scheduled visits and at unscheduled visits due to illness or suspected exposure, if necessary, information will be collected about any signs or symptoms suggestive of acute HIV infection. Participants will be counseled about signs and symptoms of acute HIV infection and at visits following recent high-risk exposure, participants will be queried about any signs/symptoms suggestive of acute HIV infection. Presence of signs/symptoms suggestive of acute HIV infection, an intercurrent illness consistent with acute retroviral syndrome, or history of high-risk exposure would prompt a diagnostic work-up per the protocol-specific algorithm for recent exposure to determine HIV infection.

8.2 HIV screening test (prior to randomization)

Prior to randomization, participants will be screened for HIV-1/2 infection by FDA-approved blood tests (non-US sites may use locally available assays that have been approved by HVTN and HPTN Laboratory Operations [see SSP]). Volunteers identified as being HIV infected during screening will be referred for medical treatment and management of the HIV infection. These individuals may also be referred to appropriate ongoing clinical trials or observational studies. For volunteers who have one or more reactive/positive HIV tests, but whose HIV status is inconclusive, any further testing will be performed locally.

8.3 HIV testing postinfusion

Following enrollment, HIV testing will take place at scheduled clinic visits ([Appendix F](#)).

HIV testing will be performed using the protocol-specific HIV testing algorithms (see SSP). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV 1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV 1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit (ie, visit #.X specified in [Appendix G](#) and [Appendix H](#)). Samples to be stored for future studies will also be collected at this time (see [Appendix G](#)).

A ‘case’ will be defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after

enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s) (Section [8.4](#)).

The HVTN Laboratory Program is responsible for all in-study diagnostic testing.

8.4 Endpoint adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess. Therefore, this study will have an endpoint adjudication process to review all serological and virological test results in a blinded manner for each participant who tests positive per the HVTN 703/HPTN 081 HIV diagnostic testing algorithms. Adjudicators will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (ie, HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the VRC and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

8.5 HIV infection during the study

It is critical to the success of the study that HIV-infected participants be properly identified and all data postdiagnosis be carefully recorded. Information obtained from these cases of HIV-1 infection will form the basis of the primary endpoint assessment.

Participants who develop HIV infection following the initial infusion of study product may remain in the study for follow-up but will receive no further infusions. This includes participants for whom infusions were discontinued for reasons other than HIV infection but for whom HIV-1 infection has subsequently been confirmed. All participants who become HIV-1–infected following enrollment through their final study visit will be monitored as indicated in [Appendix G](#) and [Appendix K](#).

If a participant is confirmed to have become HIV infected after enrollment, plasma HIV-1 RNA will be measured on archived samples prior to the first positive screening test. HIV-1 RNA testing will also be performed at 2-week intervals up to 8 weeks postdiagnosis, then at 12 and 24 weeks postdiagnosis. In addition to plasma HIV-1 RNA testing, participants will also have specimens drawn for measurements of VRC01 Ab serum levels, neutralization and other antibody functions, viral isolation and sequencing; physical exams, recording of AEs, counseling to reduce HIV transmission risk, and social impact assessments will also be performed at most of these visits.

Longer-term follow-up for these participants may be accomplished through enrollment in another protocol. Archived samples from earlier visits may also be tested to determine the earliest date of HIV infection.

If enrollment visit HIV testing indicates that a participant was HIV infected at enrollment (ie, prior to the first infusion of study product) or a participant is diagnosed with HIV-2 infection following enrollment, then the procedures indicated in the preceding paragraph do not apply. Such participants should be followed as indicated in [Appendix H](#) and [Appendix L](#). This also applies to participants for whom infusions are discontinued for reasons other than HIV infection and who subsequently are diagnosed with HIV-2 infection.

8.6 Medical care for participants who become HIV infected

It is anticipated that some study participants, whether they are randomized to receive VRC01 or control, will become HIV infected during the course of the trial. It is critical that these HIV-infected participants receive appropriate medical care.

The investigators associated with this trial will refer participants who develop HIV infection while participating in this trial to medical professionals for care.

9 Laboratory

9.1 CRS laboratory procedures

The SSP provides further guidelines for operational issues concerning the clinical and processing laboratories. This document includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in [Appendix F](#) through [Appendix I](#). For tests performed locally, the local lab may assign appropriate tube types.

In specific situations, the blood collection tubes may be redirected to another laboratory or may require study-specific processing techniques. In these cases, laboratory special instructions will be posted on the protocol-specific section of the HVTN website.

9.2 Total blood volume

Required blood volumes per visit are shown in [Appendix F](#) through [Appendix I](#). Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

9.3 Assay timepoints

Endpoint assays are performed on participants at the timepoints shown in [Appendix F](#) through [Appendix I](#) may be performed at baseline. Assays for humoral and cellular responses may be performed on participants or a subset of participants at other timepoints; the schedules are shown in [Appendix F](#) through [Appendix I](#).

9.4 VRC01 mAb levels

VRC01 levels will be measured in serum. An ELISA will be used to determine the concentration of the VRC01 antibody in the serum. The ELISA employs the VRC01 Fab-specific 5C9 mAb, which is an anti-idiotypic antibody cloned from a single B cell that was sorted by flow cytometry using a VRC01 scFv probe. The 4-parameter logistic curve regression of a standard curve of VRC01 covering the range from 0.031 to 1.0 mcg/mL is utilized in this assay to quantitate the sample concentrations based upon the average of sample dilutions within the range of the assay. This assay has been qualified but not formally validated. The functional

sensitivity for the generation of the ELISA assay format, which is currently used at NVITAL, is 2 mcg/mL and as the technology for this assay continues to develop, an updated assay may be utilized.

9.5 Endpoint assays: humoral

9.5.1 Anti-VRC01 antibody assay

Assessment for development of anti-VRC01 antibodies in participants will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. The assay uses biotin-labeled VRC01 immobilized on a streptavidin-coated MSD plate as the capture molecule, and the SULFO-TAG labeled VRC01 as the reporter molecule. This assay is independent of the anti-VRC01 antibody isotype, and permits the detection of both high and low affinity antibodies.

9.5.2 Neutralizing antibody assay

Depending upon the VRC01 concentrations measured in collected specimens, their capacity to neutralize HIV in blood and mucosal secretions may be evaluated by an in vitro cell-based virus neutralization assay [129-131] using pseudotyped viruses. All specimens testing positive for anti-VRC01 antibodies will be tested for HIV-1 neutralizing activity.

One or more viruses that are among the most sensitive to VRC01 (eg, MN.3 and MW965.26) will be assayed. The IC₅₀ of VRC01 against both of these viruses is 0.01 – 0.03 mcg/ml and the TZM-bl assay is validated for this level of sensitivity.

9.6 ARV detection

A direct, biomedical measure is used to assess ARV use in this study. This approach is used because self-report of ARV use for PrEP or PEP and other purposes has been shown to be unreliable in a variety of settings [82,132,133]. For this study, ARV testing will be performed using a test that measures the amount of tenofovir-diphosphate (a metabolite of tenofovir) in red blood cells. This test utilizes a dried blood spot as the sample source and analyzes for tenofovir diphosphate by liquid chromatography and tandem mass-spectroscopy, as previously described [134,135]. Because of a long half-life, high amounts of the metabolite in the dried blood spot correspond with consistent dosing of Truvada and low amounts correspond with inconsistent dosing [75]. Samples are collected and stored on regularly scheduled calendar days throughout the study and testing will be performed periodically on batched samples. In addition, both serum and plasma samples are collected from all participants at all timepoints. This will allow additional assessment of PrEP use by selected participants if warranted by the results of the dried blood spot assay. Individual test results will not be returned to study sites or study participants.

9.7 Host (human) genotyping

Various markers, such as genes associated with host immune functions or HIV disease progression may also be assessed.

9.8 Lab assay algorithm

The HVTN Lab Assay Algorithm lists assays that characterize various types of immunologic activity as well as host genetics that may be conducted to characterize the drug activity in this study. Various types of assays may be employed to assess maintenance of functional drug activity at multiple timepoints selected based on drug level outcomes. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

9.9 Possible additional studies

Samples may be used for other testing and research related to furthering the understanding of HIV immunology, monoclonal antibodies, or vaccines. In addition, cryopreserved samples may be used to perform additional assays to support standardization and validation of existing or newly developed methods.

9.10 Other use of stored specimens

The Networks store specimens from all study participants indefinitely, unless a participant requests that specimens be destroyed or if required by IRB/EC or RE.

Other use of specimens is defined as studies not described in the protocol.

This research may relate to HIV, vaccines, monoclonal antibodies, the immune system, and other diseases. This could include limited genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other testing on specimens will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs if required.

The protocol sample informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study site investigator or designee must notify HVTN Regulatory

Affairs in writing. In either case, HVTN Regulatory Affairs directs the HVTN Lab Program not to use samples from these participants for such other uses.

CRSs must notify HVTN Regulatory Affairs if institutional or local governmental requirements pose a conflict with or impose restrictions on other use of specimens.

9.11 Biohazard containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the CDC and the NIH or other applicable agencies.

All dangerous goods materials, including Biological Substances, Category A or Category B, must be transported according to instructions detailed in the International Air Transport Association Dangerous Goods Regulations.

10 Safety monitoring and safety review

10.1 Safety monitoring and oversight

10.1.1 HVTN 703/HPTN 081 PSRT

The HVTN 703/HPTN 081 PSRT is composed of the following members:

- DAIDS medical officer representatives,
- Protocol chairs and cochairs,
- Protocol Team leader,
- Core medical monitor,
- Clinical safety specialist (CSS), and
- Regional medical liaison (RML).

A medical officer from an organization(s) designated by the study sponsor will also participate in the PSRT.

The clinician members of HVTN 703/HPTN 081 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinators, project managers, study product developer representatives, clinical research manager, clinical trial manager, and others may also be included in HVTN 703/HPTN 081 PSRT meetings.

10.1.2 NIAID DSMB

The NIAID DSMB assesses the effects of the study product during the trial, provides other monitoring as described in Section [4.7.1.1](#), and may give advice to the HVTN 703/HPTN 081 OC.

10.1.3 Roles and responsibilities in safety monitoring

The roles and responsibilities of the SDMC in relation to safety monitoring include:

- Maintaining a central database management system for clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 703/HPTN 081 PSRT and NIAID DSMB.

The roles and responsibilities of the HVTN CSS or HVTN Core designee in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 703/HPTN 081 PSRT AE review criteria (see Section 10.3);
- Notifying CRSs and other groups when safety pauses are instituted and lifted (see Section 10.3);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 703/HPTN 081 PSRT.

10.2 Safety reporting

10.2.1 Submission of safety forms to SDMC

Sites must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, concomitant medications) before the end of the next business day after receiving the information. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information.

10.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation subject administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). The AE reporting period for this study comprises the entire study period for each individual participant (from study enrollment until study completion or discontinuation of the study). All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1. dated July 2017, available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>, except that the AEs below will be reported according to the SSP:

- Unintentional weight loss
- Infusion Site Erythema or Redness and Infusion Site Induration or Swelling
- Infusion reactions

- Uterine bleeding secondary to contraception

As detailed in the SSP, two additional parameters, cytokine release syndrome and serum sickness, have been added to the DAIDS AE Grading Table for HVTN 703/HPTN 081.

AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (Section 10.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 10.2.4).

Sites are expected to notify the CSS or RML of any serious safety concern requiring their attention (see Table 10-1). Telephone numbers and email addresses are found on the HVTN703/HPTN 081 protocol-specific website. Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, the CSS or RML will reply during working hours (ie, US Pacific Time, South Africa Standard Time, or Central Africa Time) to confirm that the email has been received and reviewed. If email service is not available, the CRS should notify the CSS or RML of the event by telephone, then submit CRFs.

In addition, site investigators are required to submit AE information in accordance with IRB/EC and any applicable RE requirements.

10.2.3 Expedited reporting of adverse events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE Manual), which is available on the RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>. The SAE Reporting Category will be used for this study.

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting>

For questions about DAERS, please contact NIAID CRMS Support at CRMSsupport@niaid.nih.gov or from within the DAERS application itself.

For questions about expedited AE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

Under ICH E2A (*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*), an SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death, if it were more severe),
- requires patient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect, or
- is a medically important event or reaction.

Medical and scientific judgment should be exercised when deciding if other situations are serious. Such instances could include medical events that may not be immediately life-threatening or result in death or hospitalization, but which may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions not resulting in hospitalization, or development of drug dependency or drug abuse.

The expedited reporting period for this study comprises the entire study period for each individual participant (from study enrolment until study completion or discontinuation from the study).

The study products for which expedited reporting are required are:

- VRC01, and
- Control.

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

If the PSRT believes unblinding of the site PI to treatment assignment will assist with the clinical management of the SAE, the PSRT may consult the independent

NIAID DSMB for a recommendation. In the event the PSRT and/or the NIAID DSMB determines that unblinding is indicated, the unblinded statistician, DSMB Chair, or designee will inform the site physician of the participant's treatment assignment in such a manner as to maintain the study blind of the PSRT and study team. For additional impact and management of SAEs on the study, refer to Section 10.3.

10.2.4 Expedited reporting of AEs to pertinent national regulatory authorities

The study sponsor or designee(s) prepares and files expedited reports to appropriate regulatory authorities within the timelines required by pertinent national regulatory authorities.

Site IoRs/designees will submit AE information and any other relevant safety information to their ECs/IRBs in accordance with EC/IRB requirements.

10.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and infusion with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 703/HPTN 081 PSRT AE review are summarized in Table 10-1. Infusions may be suspended for safety concerns other than those described in the table, or before pause rules are met, if, in the judgment of the HVTN 703/HPTN 081 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of infusions are listed in Section 5.3.

Table 10-1 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	CRS action ^a	HVTN Core ^b action
SAE, related	Grade 4 or 5	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 703/HPTN 081 PSRT notification
SAE, related	Grade 3	E-mail and submit forms immediately	Prompt HVTN 703/HPTN 081 PSRT AE review to consider pause
AE ^c , related	Grade 4 or 3	Email and submit forms immediately	Prompt HVTN 703/HPTN 081 PSRT AE review to consider pause

^a Phone numbers and email addresses are found on the Protocol home page on the HVTN Members' site (<https://members.hvtn.org/protocols/hvtn703/HPTN081>).

^b HVTN CSS or HVTN Core designee

^c Does not include subjective reactogenicity symptoms (injection site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea).

For all safety pauses, HVTN Core notifies the HVTN 703/HPTN 081 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance

Team (SPT), and participating HVTN and HPTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the NIAID DSMB.

Once a trial is paused, the HVTN 703/HPTN 081 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of infusions is appropriate, consulting the NIAID DSMB if necessary. HVTN Core notifies the participating HVTN and HPTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study infusions. Based on the HVTN 703/HPTN 081 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 703/HPTN 081 PSRT notification or prompt HVTN 703/HPTN 081 PSRT AE review is triggered, HVTN Core notifies the HVTN 703/HPTN 081 PSRT as soon as possible during working hours (US Pacific Time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 703/HPTN 081 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and an applicable RE protocol-related safety information (such as IND safety reports, notification of study product holds due to the pause rules, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 703/HPTN 081 PSRT (see Section [10.4.2](#)).

10.4 Review of cumulative safety data

Routine safety review occurs at the start of enrollment and then throughout the study.

Reviews proceed from a standardized set of protocol-specific safety data reports. These reports are produced by the SDMC and include queries to the CRSs. Events are tracked by internal reports until resolution.

10.4.1 Daily review

Blinded daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 703/HPTN 081 PSRT AE review criteria.

10.4.2 Twice monthly review

During the infusion phase of the trial, the HVTN 703/HPTN 081 PSRT reviews clinical safety reports twice each month and conducts calls to review the data as

appropriate. After the infusions and the final postinfusion safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 703/HPTN 081 PSRT. The HVTN CSS or HVTN Core designee reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

10.4.3 DSMB review of cumulative safety data

The DSMB will periodically review accumulating safety data. Prior to each such review, the SDMC will provide the DSMB with data as described in Section [4.7.1](#). Reports will be cumulative, generated from an up-to-date data file. Reports will show the data coded by treatment group; however, upon request of the DSMB, the SDMC will provide the Board with the actual treatment group.

10.5 Study termination

This study may be terminated early by NIAID upon recommendation by the DSMB, a pertinent national regulatory authority, Office for Human Research Protections (OHRP), or study product developer. In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

10.6 Social impact reporting

It is possible that participants' involvement in the study could result in social impacts. For example, a participant's involvement in the study could become known to others, and a social harm may result (ie, because participants could be perceived as being HIV infected or at "high risk" for HIV infection). Participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Alternatively, a social benefit may result (eg, a participant could feel good helping others).

Social harms are negative social impact events and social benefits are positive social impact events that a participant reports as affecting them as a result of being involved in a research study. It is not the researcher's opinion of how they perceive an event has affected a participant. Social impacts will be collected and reported on CRFs during scheduled visits (see [Appendix J](#) through [Appendix M](#)). A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. While maintaining participant confidentiality, study sites may engage their Community

Advisory Board (CAB) in exploring the social context surrounding instances of social harms to minimize the potential occurrence of such an impact.

11 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with Good Clinical Practice (GCP) (ICHe6), the HVTN and HPTN network-specific *Manuals of Operations*, and DAIDS Clinical Research Policies and Standard Procedures Documents, including procedures for the following:

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Ancillary studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the SSP.

11.1 Emergency communication with study participants

As in all clinical research, this study may generate a need to reach participants quickly to avoid imminent harm, or to report study findings that may otherwise concern their health or welfare.

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site should contact the participant first, and then notify the IRB/EC and any applicable RE of the matter as soon as possible.

12 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of clinical trials. The HVTN and HPTN (hereafter, referred to as the “Networks”) have addressed ethical concerns in the following ways:

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for preventing HIV infection, using methods that are scientifically rigorous and valid, and in accordance with GCP guidelines.
- Network scientists and operational staff incorporate the philosophies underlying major codes [136-138], declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV prevention clinical trials.
- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. CABs are required by DAIDS and supported at all Network research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines [139].
- Network clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
- The Networks require that all international Network sites lacking national plans for providing ART develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. Participants will be referred to programs for ART provision when the appropriate criteria for starting ART are met. If a program is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.
- The Networks agree that appropriate referrals for access to PrEP and PEP should be provided according to national and/or local guidelines.
- The Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have

their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.

- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.
- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.
- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.
- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.
- The Networks recognize the importance of institutional review and values the role of in country IRBs, ECs, and any applicable REs as custodians responsible for ensuring the ethical conduct of research in each setting.

13 IRB/EC/RE review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs to ensure that certain requirements are satisfied on initial and continuing review of research (Title 45, Code of Federal Regulations (CFR), Part 46.111(a) 1-7; 21 CFR 56.111(a) 1-7). The following section highlights how this protocol addresses each of these research requirements. Each Network Investigator welcomes IRB/EC and any applicable RE questions or concerns regarding these research requirements.

This trial is being conducted in Africa, with funding from the US NIH. Due to this, the trial is subject to both US and local regulations and guidelines on the protection of human research subjects and ethical research conduct. Where there is a conflict in regulations or guidelines, the regulation or guideline providing the maximum protection of human research subjects will be followed.

In compliance with international and local (as appropriate) GCP, each research location has a locally based Principal Investigator (PI) who is qualified to conduct (and supervise the conduct of) the research; and the research addresses an important local health need for an HIV prevention method. In addition, the investigators take responsibility for the conduct of the study and the control of the study products, including obtaining all appropriate regulatory and ethical reviews of the research. Each participating site has a standard operating procedure for ensuring that participants have the necessary information to make a decision whether or not to consent to the research.

The sections below address each of the review concerns by IRBs/ECs and any applicable REs regarding how the research will be conducted.

13.1 Minimized risks to participants

45 CFR 46.111 (a) 1 and 21 CFR 56.111 (a) 1: Risks to subjects are minimized.

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants following study product administration and collecting information regarding side effects for several days following study product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product infusions, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use; and (f) providing safety monitoring.

13.2 Reasonable risk/benefit balance

45 CFR 46.111(a) 2 and 21 CFR 56.111(a) 2: Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a healthy participant are not as apparent as they would be in treatment protocols, where a study participant may be ill and may have exhausted all conventional treatment options. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

13.3 Equitable subject selection

45 CFR 46.111 (a) 3 and 21 CFR 56.111 (a) 3: Subject selection is equitable

This protocol has specific inclusion and exclusion criteria for investigators to follow in admitting participants into the protocol. Participants are selected because of these criteria and not because of positions of vulnerability or privilege. Investigators are required to maintain screening and enrollment logs to document volunteers who screened into and out of the protocol and for what reasons.

13.4 Appropriate informed consent

45 CFR 46.111 (a) 4 & 5 and 21 CFR 56.111 (a) 4 & 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section [7.1](#)). Each site is provided training in informed consent by the Networks as part of its entering the respective Network. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

13.5 Adequate safety monitoring

45 CFR 46.111 (a) 6 and 21 CFR 56.111 (a) 6: There is adequate provision for monitoring the data collected to ensure the safety of subjects.

This protocol has extensive safety monitoring in place (Section 10). Safety is monitored daily by the HVTN CSS or HVTN Core designee and routinely by the HVTN 703/HPTN 081 PSRT. In addition, a DSMB periodically reviews study data.

13.6 Protect privacy/confidentiality

45 CFR 46.111 (a) 7 and 21 CFR 56.111 (a) 7: There are adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term "privacy" concerns research participants or potential research participants as individuals whereas the term "confidentiality" is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see [Appendix A](#)). The privacy of participants is protected by assigning unique identifiers in place of the participant's name on study data and specimens. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data/Specimens with the Networks and each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

14 Version history

The Protocol Team may modify the original version of the protocol. Modifications are made to Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 703/HPTN 081 are described below.

Protocol history and modifications

Date: December 14, 2017

Protocol version: Version 4.0

Protocol modification: Full Protocol Amendment 3

- Item 1 Sample size increased from 1500 to 1900
- Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

Date: August 25, 2017

Protocol version: Version 3.0

Protocol modification: Full Protocol Amendment 2

- Item 1 Revised: Study duration and participant follow-up
- Item 2 Updated in Section 1.1: Protocol team membership
- Item 3 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment
- Item 4 Updated in Sections 2.9, 2.9.3, 2.9.4, 2.10, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 5 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/preparation instructions
- Item 6 Revised in Section 4.7.3: *Monitoring for futility to assess PE*
- Item 7 Clarified in Section 5: Eligibility determination
- Item 8 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 9 Clarified in Section 6.4, *Administration*: IV bag label weight and IV tubing flushing
- Item 10 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 11 Updated in Section 7.10, *Assessments of reactogenicity*, Section 10.2.2, *AE reporting*, and Section 15, *Document references (other than literature citations)*: DAIDS AE grading table version and exceptions
- Item 12 Updated in Sections 10.2: URLs for referenced documents

- Item 13 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*
- Item 14 Updated in Section 14: *Version history*
- Item 15 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 16 Updated in Section 16: *Acronyms and abbreviations*
- Item 17 Updated in Appendix A, *Sample informed consent form*: Minimum infusion time
- Item 18 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 19 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 20 Revised in Appendix B, *Approved birth control methods (for sample informed consent form)*: Approved contraception methods
- Item 21 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoint
- Item 22 Clarified in Appendix F: DBS allowance applies to Visit and 56-day blood draw totals
- Item 23 Updated in Appendices F through I: Assay locations and HVTN laboratory listings
- Item 24 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X
- Item 25 Clarified in Appendices J and M: Provision of HIV test results
- Item 26 Added as Appendix N: Protocol signature page
- Item 27 Updated in Sections 6.2 through 6.4 per Clarification Memo 1 to protocol Version 2.0: Study product description, storage, and administration instructions
- Item 28 Corrected: Minor typographical, grammatical, and formatting errors

Date: March 8, 2017

Protocol version: Version 2.0

Protocol modification: Clarification Memo 1

- Item 1 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature
- Item 2 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation
- Item 3 Updated in Section 6.4, *Administration*: Minimum infusion time period
- Item 4 Added in Section 6.4, *Administration*: In-line filter set requirement
- Item 5 Clarified in Sections 6.3.1 and 6.3.2: VRC01 vials with visible particles not to be used

Date: June 24, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

- Item 1 Study population limited to women in sub-Saharan Africa at risk of acquiring HIV through sexual transmission
- Item 2 Added in Section 1, *Overview*: Note regarding enrollment numbers
- Item 3 Revised in Section 1, *Overview*, and Section 5.1, *Inclusion criteria*: Participant age range
- Item 4 Updated in Section 1.1, *Protocol Team*: Membership and affiliations
- Item 5 Clarified in Section 2.1, *Rationale for trial concept*: Worldwide HIV infections and licensure status of VRC01
- Item 6 Updated: Section 2.4.5, *Trial monitoring*
- Item 7 Updated: Section 2.6, *Plans for future product development and testing*
- Item 8 Added in Section 2.8.1, *Protection against challenge in NHP models*: Non-neutralizing mechanisms of bnAb protection in NHP challenge studies
- Item 9 Added in Section 2.9.2, *VRC 602*: Information on serum neutralizing activity and anti-VRC01 antibodies
- Item 10 Updated in Sections 2.9.3 and 2.9.4: Phase 1 clinical trial experience and VRC01 safety summary
- Item 11 Added in Section 2.9.3: VRC01 pharmacokinetics in HVTN 104
- Item 12 Revised in Sections 3.3, 4.8, and 9.6 and Appendix F: PrEP use monitoring
- Item 13 Revised: Section 4, *Statistical considerations*
- Item 14 Clarified in Section 5.1, *Inclusion criteria*: Urine protein measures
- Item 15 Revisions in Section 5.2: *Exclusion criteria*
- Item 16 Clarified in Section 5.3.3, *Discontinuing infusions for a participant*: Participants for whom infusions are stopped for reasons other than HIV infection
- Item 17 Updated in Section 6, *Study product preparation and administration*: Study product regimen, formulation, storage, preparation, and administration instructions
- Item 18 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications
- Item 19 Clarified in Section 7.3, *Enrollment and infusion visits*: Urine dipstick and instructions for infusion observation and reactogenicity assessment
- Item 20 Corrected in Section 7.4: *Post-infusion visits for HIV-uninfected study participants*
- Item 21 Corrected in Section 7.5, *HIV counseling and testing*: PrEP information source

- Item 22 Clarified in Section 7.5.1, *Study product-related seroreactivity*: Serum concentrations tested and reference to HIV testing only
- Item 23 Added as (new) Section 7.6: Follow-up visits for HIV-infected participants
- Item 24 Added as (new) Section 7.7 and Appendices I and M: *Follow-up for study participants for whom infusions have been stopped for reasons other than HIV infection*
- Item 25 Corrected in Section 7.8, *Contraception status*: Where to find details regarding contraception requirements
- Item 26 Clarified in Section 7.9 and Appendices F, I, J, and M: Urine testing
- Item 27 Clarified in Sections 7.10, *Assessments of reactogenicity*: Systemic and local signs and symptoms and infusion sites reactions
- Item 28 Revised in Section 7.11, *Visit windows and missed visits*: Visits for performance of safety assessments and local safety labs
- Item 29 Corrected in Section 8.5, *HIV infection during the study*: Visit schedules for HIV-infected study participants
- Item 30 Revised in Section 9.5.1, *Anti-VRC01 antibody assay*: Assay description
- Item 31 Clarified in Section 9.5.2, *Neutralizing antibody assay*: Range of applicability
- Item 32 Clarified in Section 10.1.1, *HVTN 703/HPTN 081 PSRT*: Protocol safety review team membership
- Item 33 Removed in Section 10.1.3, *Roles and responsibilities in safety monitoring*: Reference to planned holds
- Item 34 Added in Section 10.2.2, *AE reporting*: Uterine bleeding secondary to contraception
- Item 35 Added in Section 10.2.2, *AE reporting*: African working hours
- Item 36 Updated in Section 10.2.3, Expedited reporting of adverse events to DAIDS: DAERS support email address
- Item 37 Corrected in Section 10.4.2: PSRT review timing
- Item 38 Clarified in Section 10.4.3: Cumulative safety data reports to DSMB
- Item 39 Removed in Section 10.6, *Social impact reporting*: Reference to Study Specific Procedures (SSP)
- Item 40 Updated in Section 15: URL for DAIDS source documentation requirements
- Item 41 Updated and clarified: Appendix A, Sample informed consent form
- Item 42 Added in Appendix A and (optional) Appendix E: Consent for HIV-infected study participants
- Item 43 Clarified in Appendix A and C consent forms: Potential genetic testing
- Item 44 Added in Appendix A, C, and E consent forms: MCC contact information

- Item 45 Added in Appendix B, *Approved birth control methods*: Injectable contraceptives
- Item 46 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 47 Clarified in footnotes to Appendix F and J: Pregnancy testing
- Item 48 Clarified in Appendices F, G, and I: HVTN and non-HVTN endpoint laboratories
- Item 49 Added in Appendix F: VRC lab for anti-VRC01 antibody levels
- Item 50 Corrected in Appendices G, H, K, and L: Appendix titles, visit schedules, visit numbering, and procedures
- Item 51 Added in Appendices G and H: Whole blood samples for confirmatory HIV testing
- Item 52 Clarified in Appendix J, *Schedule 1—Procedures at CRS for HIV-uninfected participants*: No participant questionnaire at Visit 0 (screening visit)
- Item 53 Added to Appendices K and L: Local lab assessments
- Item 54 Updated and corrected throughout the protocol document: Acronyms, abbreviations, numbering of figures, tables, and appendices, cross-references, and grammatical errors

Date: April 15, 2016

Protocol version: Version 1.0

Protocol modification: Clarification Memo 2

- Item 1 Clarified in Appendix I, *Schedule 1—Procedures at CRS for HIV-uninfected participants*: No participant questionnaire during screening

Date: February 22, 2016

Protocol version: Version 1.0

Protocol modification: Clarification Memo 1

- Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

[Note: Clarification Memo 1 dated February 22, 2016 replaces Clarification Memo 1 dated September 4, 2015 and Letter of Amendment 1 dated September 28, 2015.]

Date: September 28, 2015

Protocol version: Version 1.0

Protocol modification: Letter of Amendment 1

- Item 1 Corrected in Appendices G, H, J, and K: Visit schedules
- Item 2 Clarified in Appendices J and K: Assessment of HIV/AIDS-related conditions applies to both complete and abbreviated physical exams

Item 3 Removed in Appendices J and K: Social impact assessment questionnaire

Date: September 4, 2015

Protocol version: Version 1.0

Protocol modification: Clarification Memo 1

Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

Item 2 Corrected: Titles of Appendices J and K

Date: August 11, 2015

Protocol version: 1.0

Protocol modification: NA

15 Document references (other than literature citations)

Other documents referred to in this protocol, and containing information relevant to the conduct of this study, include:

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at <http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf>
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at <https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures>
- Division of AIDS Protocol Registration Manual. Available at <https://www.niaid.nih.gov/sites/default/files/prmanual.pdf>
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 2.1, dated July 2017. Available at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 703/HPTN 081 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 703/HPTN 081 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/publications/dgr/Pages/index.aspx>
- HVTN Lab Assay Algorithm (available upon request)
- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects.

Available at <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

- HVTN 703/HPTN 081 Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.
- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>
- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at <https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/ClinicalSite.aspx>
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

See Section 17 for literature cited in the background and statistics sections of this protocol.

16 Acronyms and abbreviations

ACASI	audio computer assisted self-interview
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ADCVI	antibody-dependent cellular viral inhibition
AIA	anti-idiotypic antibody
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ARV	antiretroviral (drug)
AST	aspartate aminotransferase
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence intervals
CRF	case report form
CRPMC	(NIAID) Clinical Research Products Management Center
CRS*	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DSMB	(NIAID) Data and Safety Monitoring Board
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FcRn	neonatal Fc receptor
FDA	US Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FTC	emtricitabine
GC	gonorrhea
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hgb	hemoglobin

HIPAA	Health Insurance Portability and Accountability Act
HPTN	HIV Prevention Trials Network
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
IC ₅₀	inhibitory concentration (50%)
ICF	informed consent form
ICH	International Conference on Harmonisation
IgG	immunoglobulin G
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IV	intravenous
LANL	Los Alamos National Laboratory
LC	Laboratory Center
LOC	Leadership and Operations Center
mAb	monoclonal antibody
MITT	modified intent-to-treat
MSM	men who have sex with men
NDOH	(South Africa) National Department of Health
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NICD Africa)	National Institute for Communicable Diseases (Johannesburg, South
NIH	US National Institutes of Health
NVITAL	NIAID Vaccine Immune T-Cell Antibody Laboratory
OC	Oversight Committee
PBMC	peripheral blood mononuclear cell
PE	prevention efficacy
PEP	postexposure prophylaxis
PI	Principal Investigator
PK	pharmacokinetic
PMTCT	prevention of mother-to-child (HIV) transmission
PrEP	pre-exposure prophylaxis
PSRT	Protocol Safety Review Team
PYR	person year
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	(DAIDS) Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event

SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study specific procedures
STI	sexually transmitted infection
TasP	treatment as prevention
TCID ₅₀	tissue culture infectious dose (50%)
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TG	transgender
tMLE	targeted maximum likelihood estimation
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
VRC	Vaccine Research Center (NIAID)
VRP	Vaccine Research Program
WHO	World Health Organization

* CRSs were formerly referred to as HIV Vaccine Trial Units (HVTUs). Conversion to use of the term CRS is in process, and some HVTN documents may still refer to HVTUs.

17 Literature cited

1. UNAIDS. Report on the Global AIDS Epidemic, 2012 country progress reports. <http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/>. 2013. Last accessed: 2-20-2013
2. UNAIDS. Global Report: Report on the global AIDS epidemic 2013. **2013**;UNAIDS / JC2502/1/E.
3. WHO in partnership with UNICEF and UNAIDS. Global Report on HIV Treatment 2013: Results, Impact and Opportunities. **2014**.
4. UNAIDS. Local Epidemics Issues Brief. **2014**.
5. HIV/AIDS Fact Sheet. **11-2015**. <http://www.who.int/mediacentre/factsheets/fs360/en/>, accessed February 8, 2016.
6. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, Hakim JG, Kumwenda J, Grinsztejn B, Pilotto JH, Godbole SV, Mehendale S, Chariyalertsak S, Santos BR, Mayer KH, Hoffman IF, Eshleman SH, Piwowar-Manning E, Wang L, Makhema J, Mills LA, de BG, Sanne I, Eron J, Gallant J, Havlir D, Swindells S, Ribaud H, Elharrar V, Burns D, Taha TE, Nielsen-Saines K, Celentano D, Essex M, Fleming TR. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* **2011**;365:493-505.
7. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, Goicochea P, Casapia M, Guanira-Carranza JV, Ramirez-Cardich ME, Montoya-Herrera O, Fernandez T, Veloso VG, Buchbinder SP, Chariyalertsak S, Schechter M, Bekker LG, Mayer KH, Kallas EG, Amico KR, Mulligan K, Bushman LR, Hance RJ, Ganoza C, Defechereux P, Postle B, Wang F, McConnell JJ, Zheng JH, Lee J, Rooney JF, Jaffe HS, Martinez AI, Burns DN, Glidden DV. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* **2010**;363:2587-99.
8. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents: Limitations to Treatment Safety and Efficacy: Adverse Effects of Antiretroviral Agents. <http://aidsinfo.nih.gov/guidelines>. 5-1-2014. Last accessed: 2-17-2015
9. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. *AIDS* **2012**;26:F13-F19.
10. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. *Clin Infect Dis* **1992**;14:580-6.
11. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* **2006**;55:1-23.
12. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. *Curr Opin HIV AIDS* **2015**;10:129-34.

13. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. *Pediatrics* **1998**;102:531-7.
14. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, Connor EM, Losonsky GA. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. *Pediatrics* **2010**;125:e35-e51.
15. Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective. *Int J Pediatr* **2014**;2014:571609.
16. Li Y, Migueles SA, Welcher B, Svehla K, Phogat A, Louder MK, Wu X, Shaw GM, Connors M, Wyatt RT, Mascola JR. Broad HIV-1 neutralization mediated by CD4-binding site antibodies. *Nat Med* **2007**;13:1032-4.
17. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, Lehrman JK, Boaz M, Tarragona-Fiol T, Miiro G, Birungi J, Pozniak A, McPhee DA, Manigart O, Karita E, Inwoley A, Jaoko W, Dehovitz J, Bekker LG, Pitisuttithum P, Paris R, Walker LM, Poignard P, Wrin T, Fast PE, Burton DR, Koff WC. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. *J Virol* **2009**;83:7337-48.
18. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, Zhou T, Schmidt SD, Wu L, Xu L, Longo NS, McKee K, O'Dell S, Louder MK, Wycuff DL, Feng Y, Nason M, Doria-Rose N, Connors M, Kwong PD, Roederer M, Wyatt RT, Nabel GJ, Mascola JR. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. *Science* **2010**;329:856-61.
19. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, Kwon YD, Scheid JF, Shi W, Xu L, Yang Y, Zhu J, Nussenzweig MC, Sodroski J, Shapiro L, Nabel GJ, Mascola JR, Kwong PD. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. *Science* **2010**;329:811-7.
20. Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, Wibmer CK, Puren A, DeCamp A, Gilbert PB, Wood B, Montefiori DC, Binley JM, Shaw GM, Haynes BF, Mascola JR, Morris L. Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. *J Virol* **2009**;83:8925-37.
21. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, Werner L, Mlisana K, Sibeko S, Williamson C, Abdool Karim SS, Morris L. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. *J Virol* **2011**;85:4828-40.
22. Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez BM, Silacci C, Pinna D, Jarrossay D, Balla-Jhaghoorsingh S, Willems B, Zekveld MJ, Dreja H, O'Sullivan E, Pade C, Orkin C, Jeffs SA, Montefiori DC, Davis D, Weissenhorn W, McKnight A, Heeney JL, Sallusto F, Sattentau QJ, Weiss RA, Lanzavecchia A. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. *PLoS ONE* **2010**;5:e8805.

23. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, Wang SK, Ramos A, Chan-Hui PY, Moyle M, Mitcham JL, Hammond PW, Olsen OA, Phung P, Fling S, Wong CH, Phogat S, Wrin T, Simek MD, Koff WC, Wilson IA, Burton DR, Poignard P. Broad neutralization coverage of HIV by multiple highly potent antibodies. *Nature* **2011**;477:466-70.
24. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, Pietzsch J, Fenyo D, Abadir A, Velinzon K, Hurley A, Myung S, Boulad F, Poignard P, Burton DR, Pereyra F, Ho DD, Walker BD, Seaman MS, Bjorkman PJ, Chait BT, Nussenzweig MC. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. *Science* **2011**;333:1633-7.
25. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, Decker JM, Wycuff D, Harris L, Hawkins N, Wood B, Nathe C, Richman D, Tomaras GD, Bibollet-Ruche F, Robinson JE, Morris L, Shaw GM, Montefiori DC, Mascola JR. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. *J Virol* **2008**;82:11651-68.
26. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, Yu X, Wood B, Self S, Kalams S, Stamatatos L. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. *J Virol* **2009**;83:757-69.
27. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, Wu X, Seaman MS, Wrin T, Kwong PD, Wyatt RT, Mascola JR, Poignard P, Burton DR. PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. *J Virol* **2012**;86:4394-403.
28. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, Wrin T, Simek MD, Fling S, Mitcham JL, Lehrman JK, Priddy FH, Olsen OA, Frey SM, Hammond PW, Kaminsky S, Zamb T, Moyle M, Koff WC, Poignard P, Burton DR. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. *Science* **2009**;326:285-9.
29. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, Phogat SK, Poignard P, Burton DR. A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. *PLoS Pathog* **2010**;6:e1001028.
30. McLellan JS, Pancera M, Carrico C, Gorman J, Julien JP, Khayat R, Louder R, Pejchal R, Sastry M, Dai K, O'Dell S, Patel N, Shahzad-ul-Hussan S, Yang Y, Zhang B, Zhou T, Zhu J, Boyington JC, Chuang GY, Diwanji D, Georgiev I, Kwon YD, Lee D, Louder MK, Moquin S, Schmidt SD, Yang ZY, Bonsignori M, Crump JA, Kapiga SH, Sam NE, Haynes BF, Burton DR, Koff WC, Walker LM, Phogat S, Wyatt R, Orwenyo J, Wang LX, Arthos J, Bewley CA, Mascola JR, Nabel GJ, Schief WR, Ward AB, Wilson IA, Kwong PD. Structure of HIV-1 gp120 V1/V2 domain with broadly neutralizing antibody PG9. *Nature* **2011**;480:336-43.
31. Kong L, Lee JH, Doores KJ, Murin CD, Julien JP, McBride R, Liu Y, Marozsan A, Cupo A, Klasse PJ, Hoffenberg S, Caulfield M, King CR, Hua Y, Le KM, Khayat R, Deller MC, Clayton T, Tien H, Feizi T, Sanders RW, Paulson JC, Moore JP, Stanfield RL,

- Burton DR, Ward AB, Wilson IA. Supersite of immune vulnerability on the glycosylated face of HIV-1 envelope glycoprotein gp120. *Nat Struct Mol Biol* **2013**;20:796-803.
32. Huang J, Ofek G, Laub L, Louder MK, Doria-Rose NA, Longo NS, Imamichi H, Bailer RT, Chakrabarti B, Sharma SK, Alam SM, Wang T, Yang Y, Zhang B, Migueles SA, Wyatt R, Haynes BF, Kwong PD, Mascola JR, Connors M. Broad and potent neutralization of HIV-1 by a gp41-specific human antibody. *Nature* **2012**;491:406-12.
33. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? *Nat Med* **2009**;15:866-70.
34. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. *Curr Opin Immunol* **2010**;22:358-66.
35. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, Kaufmann DE, McElrath MJ, Nussenzweig MC, Pulendran B, Scanlan CN, Schief WR, Silvestri G, Streeck H, Walker BD, Walker LM, Ward AB, Wilson IA, Wyatt R. A Blueprint for HIV Vaccine Discovery. *Cell Host Microbe* **2012**;12:396-407.
36. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. *Proc Natl Acad Sci U S A* **2005**;102:14943-8.
37. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. *Immunity* **2012**;37:412-25.
38. Georgiev IS, Gordon JM, Zhou T, Kwong PD. Elicitation of HIV-1-neutralizing antibodies against the CD4-binding site. *Curr Opin HIV AIDS* **2013**;8:382-92.
39. Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, Imamichi H, Doria-Rose N, Hoxie JA, Connors M, Shaw GM, Wyatt RT, Mascola JR. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. *J Virol* **2012**;86:5844-56.
40. Shibata R, Igarashi T, Haigwood N, Buckler-White A, Ogert R, Ross W, Willey R, Cho MW, Martin MA. Neutralizing antibody directed against the HIV-1 envelope glycoprotein can completely block HIV-1/SIV chimeric virus infections of macaque monkeys. *Nat Med* **1999**;5:204-10.
41. Baba TW, Liska V, Hofmann-Lehmann R, Vlasak J, Xu W, Ayehunie S, Cavacini LA, Posner MR, Katinger H, Stiegler G, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Lu Y, Wright JE, Chou TC, Ruprecht RM. Human neutralizing monoclonal antibodies of the IgG1 subtype protect against mucosal simian-human immunodeficiency virus infection. *Nat Med* **2000**;6:200-6.
42. Hofmann-Lehmann R, Vlasak J, Rasmussen RA, Jiang S, Li PL, Baba TW, Montefiori DC, Bernacky BJ, Rizvi TA, Schmidt R, Hill LR, Keeling ME, Katinger H, Stiegler G, Cavacini LA, Posner MR, Ruprecht RM. Postnatal pre- and postexposure passive immunization strategies: protection of neonatal macaques against oral simian-human immunodeficiency virus challenge. *J Med Primatol* **2002**;31:109-19.

43. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
44. Hessel AJ, Rakasz EG, Poignard P, Hangartner L, Landucci G, Forthal DN, Koff WC, Watkins DI, Burton DR. Broadly neutralizing human anti-HIV antibody 2G12 is effective in protection against mucosal SHIV challenge even at low serum neutralizing titers. *PLoS Pathog* **2009**;5:e1000433.
45. Hessel AJ, Poignard P, Hunter M, Hangartner L, Tehrani DM, Bleeker WK, Parren PW, Marx PA, Burton DR. Effective, low-titer antibody protection against low-dose repeated mucosal SHIV challenge in macaques. *Nat Med* **2009**;15:951-4.
46. Moldt B, Rakasz EG, Schultz N, Chan-Hui PY, Swiderek K, Weisgrau KL, Piaskowski SM, Bergman Z, Watkins DI, Poignard P, Burton DR. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. *Proc Natl Acad Sci U S A* **2012**;109:18921-5.
47. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, McKee K, Kong WP, Shi W, Chen X, Todd JP, Letvin NL, Huang J, Nason MC, Hoxie JA, Kwong PD, Connors M, Rao SS, Mascola JR, Nabel GJ. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. *Sci Transl Med* **2014**;6:243ra88.
48. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, Wang K, Bao S, Kraemer TD, Rath T, Zeng M, Schmidt SD, Todd JP, Penzak SR, Saunders KO, Nason MC, Haase AT, Rao SS, Blumberg RS, Mascola JR, Nabel GJ. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. *Nature* **2014**;514:642-5.
49. Rudicell RS, Kwon YD, Ko SY, Pegu A, Louder MK, Georgiev IS, Wu X, Zhu J, Boyington JC, Chen X, Shi W, Yang ZY, Doria-Rose NA, McKee K, O'Dell S, Schmidt SD, Chuang GY, Druz A, Soto C, Yang Y, Zhang B, Zhou T, Todd JP, Lloyd KE, Eudailey J, Roberts KE, Donald BR, Bailer RT, Ledgerwood J, Mullikin JC, Shapiro L, Koup RA, Graham BS, Nason MC, Connors M, Haynes BF, Rao SS, Roederer M, Kwong PD, Mascola JR, Nabel GJ. Enhanced potency of a broadly neutralizing HIV-1 antibody in vitro improves protection against lentiviral infection in vivo. *J Virol* **2014**;88:12669-82.
50. Florese RH, Demberg T, Xiao P, Kuller L, Larsen K, Summers LE, Venzon D, Cafaro A, Ensoli B, Robert-Guroff M. Contribution of nonneutralizing vaccine-elicited antibody activities to improved protective efficacy in rhesus macaques immunized with Tat/Env compared with multigenic vaccines. *J Immunol* **2009**;182:3718-27.
51. Forthal DN, Landucci G, Phan TB, Becerra J. Interactions between natural killer cells and antibody Fc result in enhanced antibody neutralization of human immunodeficiency virus type 1. *J Virol* **2005**;79:2042-9.
52. Asmal M, Sun Y, Lane S, Yeh W, Schmidt SD, Mascola JR, Letvin NL. Antibody-dependent cell-mediated viral inhibition emerges after simian immunodeficiency virus

SIVmac251 infection of rhesus monkeys coincident with gp140-binding antibodies and is effective against neutralization-resistant viruses. *J Virol* **2011**;85:5465-75.

53. Tudor D, Derrien M, Diomedea L, Drillet AS, Houimel M, Moog C, Reynes JM, Lopalco L, Bomsel M. HIV-1 gp41-specific monoclonal mucosal IgAs derived from highly exposed but IgG-seronegative individuals block HIV-1 epithelial transcytosis and neutralize CD4(+) cell infection: an IgA gene and functional analysis. *Mucosal Immunol* **2009**;2:412-26.
54. Doria-Rose NA, Schramm CA, Gorman J, Moore PL, Bhiman JN, DeKosky BJ, Ernandes MJ, Georgiev IS, Kim HJ, Pancera M, Staupe RP, Altae-Tran HR, Bailer RT, Crooks ET, Cupo A, Druz A, Garrett NJ, Hoi KH, Kong R, Louder MK, Longo NS, McKee K, Nonyane M, O'Dell S, Roark RS, Rudicell RS, Schmidt SD, Sheward DJ, Soto C, Wibmer CK, Yang Y, Zhang Z, Mullikin JC, Binley JM, Sanders RW, Wilson IA, Moore JP, Ward AB, Georgiou G, Williamson C, Abdool Karim SS, Morris L, Kwong PD, Shapiro L, Mascola JR. Developmental pathway for potent V1V2-directed HIV-neutralizing antibodies. *Nature* **2014**;509:55-62.
55. Pancera M, Shahzad-ul-Hussan S, Doria-Rose NA, McLellan JS, Bailer RT, Dai K, Loesgen S, Louder MK, Staupe RP, Yang Y, Zhang B, Parks R, Eudailey J, Lloyd KE, Blinn J, Alam SM, Haynes BF, Amin MN, Wang LX, Burton DR, Koff WC, Nabel GJ, Mascola JR, Bewley CA, Kwong PD. Structural basis for diverse N-glycan recognition by HIV-1-neutralizing V1-V2-directed antibody PG16. *Nat Struct Mol Biol* **2013**;20:804-13.
56. Zhou T, Lynch RM, Chen L, Acharya P, Wu X, Doria-Rose NA, Joyce MG, Lingwood D, Soto C, Bailer RT, Ernandes MJ, Kong R, Longo NS, Louder MK, McKee K, O'Dell S, Schmidt SD, Tran L, Yang Z, Druz A, Luongo TS, Moquin S, Srivatsan S, Yang Y, Zhang B, Zheng A, Pancera M, Kirys T, Georgiev IS, Gindin T, Peng HP, Yang AS, Mullikin JC, Gray MD, Stamatatos L, Burton DR, Koff WC, Cohen MS, Haynes BF, Casazza JP, Connors M, Corti D, Lanzavecchia A, Sattentau QJ, Weiss RA, West AP, Jr., Bjorkman PJ, Scheid JF, Nussenzweig MC, Shapiro L, Mascola JR, Kwong PD. Structural Repertoire of HIV-1-Neutralizing Antibodies Targeting the CD4 Supersite in 14 Donors. *Cell* **2015**;161:1280-92.
57. Chuang GY, Acharya P, Schmidt SD, Yang Y, Louder MK, Zhou T, Kwon YD, Pancera M, Bailer RT, Doria-Rose NA, Nussenzweig MC, Mascola JR, Kwong PD, Georgiev IS. Residue-level prediction of HIV-1 antibody epitopes based on neutralization of diverse viral strains. *J Virol* **2013**;87:10047-58.
58. Derdeyn CA, Decker JM, Bibollet-Ruche F, Mokili JL, Muldoon M, Denham SA, Heil ML, Kasolo F, Musonda R, Hahn BH, Shaw GM, Korber BT, Allen S, Hunter E. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* **2004**;303:2019-22.
59. Wilen CB, Parrish NF, Pfaff JM, Decker JM, Henning EA, Haim H, Petersen JE, Wojcechowskyj JA, Sodroski J, Haynes BF, Montefiori DC, Tilton JC, Shaw GM, Hahn BH, Doms RW. Phenotypic and immunologic comparison of clade B transmitted/founder and chronic HIV-1 envelope glycoproteins. *J Virol* **2011**;85:8514-27.
60. UNAIDS. The GAP Report. **2014**.

61. Padian NS, van der SA, Ramjee G, Chipato T, de Bruyn G, Blanchard K, Shiboski S, Montgomery ET, Fancher H, Cheng H, Rosenblum M, van der LM, Jewell N, McIntyre J. Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial. *Lancet* **2007**;370:251-61.
62. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, Cowan F, Casapia M, Ortiz A, Fuchs J, Buchbinder S, Koblin B, Zwerski S, Rose S, Wang J, Corey L. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet* **2008**;371:2109-19.
63. Gray GE, Allen M, Moodie Z, Churchyard G, Bekker LG, Nchabeleng M, Mlisana K, Metch B, de BG, Latka MH, Roux S, Mathebula M, Naicker N, Ducar C, Carter DK, Puren A, Eaton N, McElrath MJ, Robertson M, Corey L, Kublin JG. Safety and efficacy of the HVTN 503/Phambili study of a clade-B-based HIV-1 vaccine in South Africa: a double-blind, randomised, placebo-controlled test-of-concept phase 2b study. *Lancet Infect Dis* **2011**;11:507-15.
64. Gray GE, Moodie Z, Metch B, Gilbert PB, Bekker LG, Churchyard G, Nchabeleng M, Mlisana K, Laher F, Roux S, Mngadi K, Innes C, Mathebula M, Allen M, McElrath MJ, Robertson M, Kublin J, Corey L. Recombinant adenovirus type 5 HIV gag/pol/nef vaccine in South Africa: unblinded, long-term follow-up of the phase 2b HVTN 503/Phambili study. *Lancet Infect Dis* **2014**;14:388-96.
65. Abdool KQ, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, Kharsany AB, Sibeko S, Mlisana KP, Omar Z, Gengiah TN, Maarschalk S, Arulappan N, Mlotshwa M, Morris L, Taylor D. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science* **2010**;329:1168-74.
66. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, Malahleha M, Owino F, Manongi R, Onyango J, Temu L, Monedi MC, Mak'Oketch P, Makanda M, Reblin I, Makatu SE, Saylor L, Kiernan H, Kirkendale S, Wong C, Grant R, Kashuba A, Nanda K, Mandala J, Fransen K, Deese J, Crucitti T, Mastro TD, Taylor D. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2012**;367:411-22.
67. NIAID. Daily-Use HIV Prevention Approaches Prove Ineffective Among Women in NIH Study. <http://www.niaid.nih.gov/news/newsreleases/2013/Pages/VOICEwomen.aspx>. 3-4-2013
68. World Medical Association. Ethical Principles for Medical Research Involving Human Subjects, Note of Clarification on Paragraph 29. **2002**.
69. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA* **2000**;283:2701-11.
70. Emanuel EJ, Miller FG. The ethics of placebo-controlled trials--a middle ground. *N Engl J Med* **2001**;345:915-9.
71. Ng CT, Jaworski JP, Jayaraman P, Sutton WF, Delio P, Kuller L, Anderson D, Landucci G, Richardson BA, Burton DR, Forthal DN, Haigwood NL. Passive neutralizing antibody

controls SHIV viremia and enhances B cell responses in infant macaques. *Nat Med* **2010**;16:1117-9.

72. Lynch RM, Wong P, Tran L, O'Dell S, Nason MC, Li Y, Wu X, Mascola JR. HIV-1 fitness cost associated with escape from the VRC01 class of CD4 binding site neutralizing antibodies. *J Virol* **2015**;89:4201-13.
73. Gilbert PB, Grove D, Gabriel E, Huang Y, Gray G, Hammer SM, Buchbinder SP, Kublin J, Corey L, Self SG. A Sequential Phase 2b Trial Design for Evaluating Vaccine Efficacy and Immune Correlates for Multiple HIV Vaccine Regimens. *Stat Commun Infect Dis* **2011**;3.
74. Kamb ML, Fishbein M, Douglas JM, Jr., Rhodes F, Rogers J, Bolan G, Zenilman J, Hoxworth T, Malotte CK, Iatesta M, Kent C, Lentz A, Graziano S, Byers RH, Peterman TA. Efficacy of risk-reduction counseling to prevent human immunodeficiency virus and sexually transmitted diseases: a randomized controlled trial. Project RESPECT Study Group. *JAMA* **1998**;280:1161-7.
75. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, Hosek S, Mosquera C, Casapia M, Montoya O, Buchbinder S, Veloso VG, Mayer K, Chariyalertsak S, Bekker LG, Kallas EG, Schechter M, Guanira J, Bushman L, Burns DN, Rooney JF, Glidden DV. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. *Lancet Infect Dis* **2014**;14:820-9.
76. McCormack S, Dunn DT, Desai M, Dolling DI, Gafos M, Gilson R, Sullivan AK, Clarke A, Reeves I, Schembri G, Mackie N, Bowman C, Lacey CJ, Apea V, Brady M, Fox J, Taylor S, Antonucci S, Khoo SH, Rooney J, Nardone A, Fisher M, McOwan A, Phillips AN, Johnson AM, Gazzard B, Gill ON. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. *Lancet* **2015**.
77. McCormack S, Dunn D. Pragmatic open-label randomized trial of preexposure prophylaxis: The PROUD study (Abstract 22LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
78. Molina J-M, Capitant C, Charreau I, Meyer L, Spire B, Pialoux G, Chidiac C, Delfraissy J-F, Tremblay C. On demand PrEP with Oral TDF-FTC in MSM: Results of the ANRS Ipergay trial (Abstract 23LB) . Conference on Retroviruses and Opportunistic Infections, Seattle, Washington (USA), February 23-26, **2015**
79. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, Tremblay C, Le Gall JM, Cua E, Pasquet A, Raffi F, Pintado C, Chidiac C, Chas J, Charbonneau P, Delaugerre C, Suzan-Monti M, Loze B, Fonsart J, Peytavin G, Cheret A, Timsit J, Girard G, Lorente N, Preau M, Rooney JF, Wainberg MA, Thompson D, Rozenbaum W, Dore V, Marchand L, Simon MC, Etien N, Aboulker JP, Meyer L, Delfraissy JF. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* **2015**;373:2237-46.
80. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, Tappero JW, Bukusi EA, Cohen CR, Katabira E, Ronald A, Tumwesigye E, Were E, Fife KH, Kiarie J, Farquhar C, John-Stewart G, Kakia A, Odoyo J, Mucunguzi A, Nakku-Joloba E,

- Twesigye R, Ngure K, Apaka C, Tamoo H, Gabona F, Mujugira A, Panteleeff D, Thomas KK, Kidoguchi L, Krows M, Revall J, Morrison S, Haugen H, Emmanuel-Ogier M, Ondrejcek L, Coombs RW, Frenkel L, Hendrix C, Bumpus NN, Bangsberg D, Haberer JE, Stevens WS, Lingappa JR, Celum C. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* **2012**;367:399-410.
81. Rees, H, Delany-Moretlwa, S, Baron, D, Lombard, C, Gray, G, Myers, L, Panchia, R, Schwartz, J, and Doncel, G. FACTS 001 Phase III trial of pericoital Tenofovir 1% gel for HIV prevention in women (Abstract 26LB).
<http://www.croiconference.org/sessions/facts-001-phase-iii-trial-pericoital-tenofovir-1-gel-hiv-prevention-women>. 2015. Last accessed: 6-15-2015
82. Marrazzo JM, Ramjee G, Richardson BA, Gomez K, Mgodini N, Nair G, Palanee T, Nakabiito C, van der Straten A, Noguchi L, Hendrix CW, Dai JY, Ganesh S, Mkhize B, Taljaard M, Parikh UM, Piper J, Masse B, Grossman C, Rooney J, Schwartz JL, Watts H, Marzinke MA, Hillier SL, McGowan IM, Chirenje ZM. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* **2015**;372:509-18.
83. Hanscom B, Janes H, Guarino P, Huang Y, Brown E, Ying Q, Hammer S, Gilbert P, Donnell D. Is oral PrEP effective in preventing HIV in women? **2015**.
84. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, Cohen MS, Kashuba AD. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med* **2011**;3:112re4.
85. Cottrell ML, Yang KH, Prince HM, Sykes C, White N, Malone S, Dellon ES, Madanick RD, Shaheen NJ, Hudgens MG, Wulff J, Patterson KB, Nelson JA, Kashuba AD. A Translational Pharmacology Approach to Predicting HIV Pre-Exposure Prophylaxis Outcomes in Men and Women Using Tenofovir Disoproxil Fumarate+/-Emtricitabine. *J Infect Dis* **2016**.
86. Centers for Disease Control and Prevention. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex With Men.
<http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6003a1.htm>. 1-28-2011. Last accessed: 4-10-2015
87. World Health Organization. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV. July 2012. **2012**.
88. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: A Clinical Practice Guideline. **2014**.
89. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States - 2014: Clinical Providers' Supplement. 2014. US Centers for Disease Control and Prevention.
90. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach.
<http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>. 6-30-2013. Last accessed: 2-2-2015

91. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. **2015**.
92. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, Gupta S, Herzyk D, Hurst C, Ivens IA, Kawabata T, Maier C, Mounho B, Rup B, Shankar G, Smith H, Thomas P, Wierda D. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol* **2009**;54:164-82.
93. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci* **2004**;93:2645-68.
94. Li Y, O'Dell S, Walker LM, Wu X, Guenaga J, Feng Y, Schmidt SD, McKee K, Louder MK, Ledgerwood JE, Graham BS, Haynes BF, Burton DR, Wyatt RT, Mascola JR. Mechanism of neutralization by the broadly neutralizing HIV-1 monoclonal antibody VRC01. *J Virol* **2011**;85:8954-67.
95. Haynes BF, Fleming J, St Clair EW, Katinger H, Stiegler G, Kunert R, Robinson J, Searce RM, Plonk K, Staats HF, Ortel TL, Liao HX, Alam SM. Cardiolipin polyspecific autoreactivity in two broadly neutralizing HIV-1 antibodies. *Science* **2005**;308:1906-8.
96. Mascola JR, Lewis MG, Stiegler G, Harris D, VanCott TC, Hayes D, Louder MK, Brown CR, Sapan CV, Frankel SS, Lu Y, Robb ML, Katinger H, Birx DL. Protection of Macaques against pathogenic simian/human immunodeficiency virus 89.6PD by passive transfer of neutralizing antibodies. *J Virol* **1999**;73:4009-18.
97. Mascola JR, Stiegler G, VanCott TC, Katinger H, Carpenter CB, Hanson CE, Beary H, Hayes D, Frankel SS, Birx DL, Lewis MG. Protection of macaques against vaginal transmission of a pathogenic HIV-1/SIV chimeric virus by passive infusion of neutralizing antibodies. *Nat Med* **2000**;6:207-10.
98. Mascola JR. Defining the protective antibody response for HIV-1. *Curr Mol Med* **2003**;3:209-16.
99. Nishimura Y, Igarashi T, Haigwood N, Sadjadpour R, Plishka RJ, Buckler-White A, Shibata R, Martin MA. Determination of a statistically valid neutralization titer in plasma that confers protection against simian-human immunodeficiency virus challenge following passive transfer of high-titered neutralizing antibodies. *J Virol* **2002**;76:2123-30.
100. Parren PW, Marx PA, Hessel AJ, Luckay A, Harouse J, Cheng-Mayer C, Moore JP, Burton DR. Antibody protects macaques against vaginal challenge with a pathogenic R5 simian/human immunodeficiency virus at serum levels giving complete neutralization in vitro. *J Virol* **2001**;75:8340-7.
101. Sadjadpour R, Donau OK, Shingai M, Buckler-White A, Kao S, Strebel K, Nishimura Y, Martin MA. Emergence of gp120 V3 variants confers neutralization resistance in an R5 simian-human immunodeficiency virus-infected macaque elite neutralizer that targets the N332 glycan of the human immunodeficiency virus type 1 envelope glycoprotein. *J Virol* **2013**;87:8798-804.
102. Gautam R, Nishimura Y, Lee WR, Donau O, Buckler-White A, Shingai M, Sadjadpour R, Schmidt SD, LaBranche CC, Keele BF, Montefiori D, Mascola JR, Martin MA.

Pathogenicity and mucosal transmissibility of the R5-tropic simian/human immunodeficiency virus SHIV(AD8) in rhesus macaques: implications for use in vaccine studies. *J Virol* **2012**;86:8516-26.

103. Shingai M, Donau OK, Plishka RJ, Buckler-White A, Mascola JR, Nabel GJ, Nason MC, Montefiori D, Moldt B, Poignard P, Diskin R, Bjorkman PJ, Eckhaus MA, Klein F, Mouquet H, Cetrulo Lorenzi JC, Gazumyan A, Burton DR, Nussenzweig MC, Martin MA, Nishimura Y. Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques. *J Exp Med* **2014**;211:2061-74.
104. Hessel AJ, Hangartner L, Hunter M, Havenith CE, Beurskens FJ, Bakker JM, Lanigan CM, Landucci G, Forthal DN, Parren PW, Marx PA, Burton DR. Fc receptor but not complement binding is important in antibody protection against HIV. *Nature* **2007**;449:101-4.
105. Saunders KO, Pegu A, Georgiev IS, Zeng M, Joyce MG, Yang ZY, Ko SY, Chen X, Schmidt SD, Haase AT, Todd JP, Bao S, Kwong PD, Rao SS, Mascola JR, Nabel GJ. Sustained Delivery of a Broadly Neutralizing Antibody in Nonhuman Primates Confers Long-Term Protection against Simian/Human Immunodeficiency Virus Infection. *J Virol* **2015**;89:5895-903.
106. Lynch RM, Boritz E, Coates EE, DeZure A, Madden P, Costner P, Enama ME, Plummer S, Holman L, Hendel CS, Gordon I, Casazza J, Conan-Cibotti M, Migueles SA, Tressler R, Bailer RT, McDermott A, Narpala S, O'Dell S, Wolf G, Lifson JD, Freemire BA, Gorelick RJ, Pandey JP, Mohan S, Chomont N, Fromentin R, Chun TW, Fauci AS, Schwartz RM, Koup RA, Douek DC, Hu Z, Capparelli E, Graham BS, Mascola JR, Ledgerwood JE. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. *Sci Transl Med* **2015**;7:319ra206.
107. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, DeZure A, Lynch RM, Gordon I, Plummer S, Hendel CS, Pegu A, Conan-Cibotti M, Sitar S, Bailer RT, Narpala S, McDermott A, Louder M, O'Dell S, Mohan S, Pandey JP, Schwartz RM, Hu Z, Koup RA, Capparelli E, Mascola JR, Graham BS. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. *Clin Exp Immunol* **2015**;182:289-301.
108. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. *Nat Rev Drug Discov* **2010**;9:325-38.
109. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. *Expert Rev Clin Immunol* **2009**;5:499-521.
110. Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* **2010**;14:E10-E21.
111. Rosenbaum P. The consequences of adjustment for a concomitant variable that has been affected by the treatment. *Journal of the Royal Statistical Society, Series A (General)* **1984**;147:656-66.

112. Joffe MM, Greene T. Related causal frameworks for surrogate outcomes. *Biometrics* **2009**;65:530-8.
113. Follmann D. Augmented designs to assess immune response in vaccine trials. *Biometrics* **2006**;62:1161-9.
114. Gilbert PB, Hudgens MG. Evaluating candidate principal surrogate endpoints. *Biometrics* **2008**;64:1146-54.
115. Huang Y, Gilbert PB, Wolfson J. Design and estimation for evaluating principal surrogate markers in vaccine trials. *Biometrics* **2013**;69:301-9.
116. Rida W, Fast P, Hoff R, Fleming T. Intermediate-size trials for the evaluation of HIV vaccine candidates: a workshop summary. *J Acquir Immune Defic Syndr Hum Retrovirol* **1997**;16:195-203.
117. Juraska, M, Grove, D, Yu, X, and Gilbert, PG. seqDesign: Simulation and Group Sequential Monitoring of Randomized Two-Stage Treatment Efficacy Trials with Time-to-Event Endpoints. R package version 1.1. <http://CRAN.R-project.org?package=seqDesign>. 4-27-2015. Last accessed: 5-15-2015
118. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, Henderson FL, Pathak SR, Soud FA, Chillag KL, Mutanhaurwa R, Chirwa LI, Kasonde M, Abebe D, Buliva E, Gvetadze RJ, Johnson S, Sukalac T, Thomas VT, Hart C, Johnson JA, Malotte CK, Hendrix CW, Brooks JT. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* **2012**;367:423-34.
119. Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* **1985**;4:213-26.
120. Freidlin B, Korn EL, Gray R. A general inefficacy interim monitoring rule for randomized clinical trials. *Clin Trials* **2010**;7:197-208.
121. Hammer SM, Sobieszczyk ME, Janes H, Karuna ST, Mulligan MJ, Grove D, Koblin BA, Buchbinder SP, Keefer MC, Tomaras GD, Frahm N, Hural J, Anude C, Graham BS, Enama ME, Adams E, DeJesus E, Novak RM, Frank I, Bentley C, Ramirez S, Fu R, Koup RA, Mascola JR, Nabel GJ, Montefiori DC, Kublin J, McElrath MJ, Corey L, Gilbert PB. Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine. *N Engl J Med* **2013**;369:2083-92.
122. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* **1983**;39:499-503.
123. Kalbfleisch J, Prentice R. *The Statistical Analysis of Failure Time Data (Second Edition)*. John Wiley & Sons, Inc., **2002**.
124. Moore K, van der Laan M. Application of time-to-event methods in the assessment of safety in clinical trials. U. C. Berkeley Division of Biostatistics Working Paper Series, Paper 248. 2009.
125. van der Laan M, Rose S. *Targeted Learning: Causal Inference for Observational and Experimental Data*. Springer, **2011**.

126. Gilbert PB, Wei LJ, Kosorok MR, Clemens JD. Simultaneous inferences on the contrast of two hazard functions with censored observations. *Biometrics* **2002**;58:773-80.
127. Edlefsen P, Magaret C, Poon A, Matsen I, Eller L, Tovanabutra S, Chopera D, Labuschagne P, Warth C, Holzman T, Rossenkahn R, Abrahams M-R, Logan M, Anthony C, Botha G, Matten D, Nitayaphan S, Rono K, Sekiziyivu A, Ndabambi N, Travers S, Michael N, Williamson C, Robb N, Gilbert P. Systematic evaluation of HIV infection time and founder inferences using SGA and Illumina sequences . Keystone Symposia on Molecular and Cellular Biology, HIV Vaccines (X8), Olympic Valley, California, USA, March 20-24, 2016, **2016**
128. Gilbert P, Wang M, Wrin T, Petropoulos C, Gurwith M, Sinangil F, D'Souza P, Rodriguez-Chavez IR, DeCamp A, Giganti M, Berman PW, Self SG, Montefiori DC. Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine. *J Infect Dis* **2010**;202:595-605.
129. Montefiori DC. Measuring HIV neutralization in a luciferase reporter gene assay. *Methods Mol Biol* **2009**;485:395-405.
130. Todd CA, Greene KM, Yu X, Ozaki DA, Gao H, Huang Y, Wang M, Li G, Brown R, Wood B, D'Souza MP, Gilbert P, Montefiori DC, Sarzotti-Kelsoe M. Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells. *J Immunol Methods* **2012**;375:57-67.
131. Ozaki DA, Gao H, Todd CA, Greene KM, Montefiori DC, Sarzotti-Kelsoe M. International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials. *PLoS ONE* **2012**;7:e30963.
132. Fogel JM, Wang L, Parsons TL, Ou SS, Piwovar-Manning E, Chen Y, Mudhune VO, Hosseinipour MC, Kumwenda J, Hakim JG, Chariyalertsak S, Panchia R, Sanne I, Kumarasamy N, Grinsztejn B, Makhema J, Pilotto J, Santos BR, Mayer KH, McCauley M, Gamble T, Bumpus NN, Hendrix CW, Cohen MS, Eshleman SH. Undisclosed antiretroviral drug use in a multinational clinical trial (HIV Prevention Trials Network 052). *J Infect Dis* **2013**;208:1624-8.
133. Marzinke MA, Clarke W, Wang L, Cummings V, Liu TY, Piwovar-Manning E, Breaud A, Griffith S, Buchbinder S, Shoptaw S, Del RC, Magnus M, Mannheimer S, Fields SD, Mayer KH, Wheeler DP, Koblin BA, Eshleman SH, Fogel JM. Nondisclosure of HIV status in a clinical trial setting: antiretroviral drug screening can help distinguish between newly diagnosed and previously diagnosed HIV infection. *Clin Infect Dis* **2014**;58:117-20.
134. Castillo-Mancilla JR, Zheng JH, Rower JE, Meditz A, Gardner EM, Predhomme J, Fernandez C, Langness J, Kiser JJ, Bushman LR, Anderson PL. Tenofovir, emtricitabine, and tenofovir diphosphate in dried blood spots for determining recent and cumulative drug exposure. *AIDS Res Hum Retroviruses* **2013**;29:384-90.
135. Bushman LR, Kiser JJ, Rower JE, Klein B, Zheng JH, Ray ML, Anderson PL. Determination of nucleoside analog mono-, di-, and tri-phosphates in cellular matrix by solid phase extraction and ultra-sensitive LC-MS/MS detection. *J Pharm Biomed Anal* **2011**;56:390-401.

136. UNAIDS. Ethical considerations in biomedical HIV prevention trials. **2007**.
137. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. **1979**.
138. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics **2002**;17-23.
139. UNAIDS/JC1853E (Second edition J2. Good participatory practice: Guidelines for biomedical HIV prevention trials. 2011.

Appendix A Sample informed consent form

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

Protocol number: HVTN 703/HPTN 081, The AMP Study

Site: [Insert site name]

Thank you for your interest in our research study. Please read this consent form or ask someone to read it to you. If you decide to join the study, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

Research is not the same as treatment or medical care. The purpose of a research study is to answer scientific questions.

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN), and [Insert site name] are doing a study to test the antibody called VRC01 against HIV. HIV is the virus that causes AIDS. Antibodies are one of the natural ways the body fights infection. Researchers can also make antibodies in laboratories and give them to people intravenously (with an IV). We will tell you more about this procedure below. This has been done successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 1900 people will take part in this study at multiple sites in Africa. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

In addition, a similar study will be done with 2700 men and transgender people who have sex with men and transgender people in the North America, South America, and Switzerland.

1. We are doing this study to answer several questions.

- Is the antibody safe to give to people?
- Are people able to take the antibody without becoming too uncomfortable?
- Does the antibody lower people's chances of getting infected with HIV?
- If the antibody does lower people's chances of getting infected with HIV, how much of it is needed to provide protection from HIV?

2. The antibody cannot give you HIV.

It is impossible for the antibody to give you HIV. Also, it cannot cause you to give HIV to someone else. However, we do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. The antibody is experimental.

The antibody being tested is called VRC-HIVMAB060-00-AB. It is an antibody against the HIV virus. From here on, we will call it VRC01 or the antibody. It is an experimental product. That means we do not know whether the antibody will be safe to use in people, or whether it will work to prevent HIV infection. This antibody is used only in research studies.

VRC01 was developed by the Vaccine Research Center at the US National Institutes of Health (NIH).

In laboratory and animal studies, VRC01 attached to and prevented infection by many strains of HIV viruses from around the world. We do not know if antibodies can prevent HIV infection when they are given to people. This study is designed to help answer that question. At this time there are no plans to make VRC01 for sale.

Risks of VRC01 antibody:

As of April 2017, VRC01 has been given to people in 12 clinical studies in the United States, Peru, Brazil, Switzerland, and in sub-Saharan Africa. In these studies, more than 1800 adults and 33 infants have gotten VRC01 or a placebo (a liquid with no antibody in it).

Many of these studies are still going on and we don't know which people got VRC01 and which got a placebo. In early trials, more than 100 people got VRC01 and it did not make them too uncomfortable or cause serious health problems. After receiving the antibody, most people said that they had mild pain, itching, or redness where the antibody was given to them. Of these people, some said they felt like they had the flu after getting the antibody, but that this feeling lasted a few hours at most.

In a previous study, one person who got a VRC01 injection had a rash. One person had a brief fainting spell several hours after getting a VRC01 infusion. To be safe, no more injections or infusions were given to these people. Some participants had mild body discomfort, muscle pain, or joint pain after getting the VRC01 antibody.

VRC01 may have other side effects that we do not know about yet.

General risks of antibodies:

Antibodies that are different from VRC01 have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat or chest pain.

Rarely, some antibodies have caused serious reactions. These reactions may be life-threatening. Please tell us if you have ever had any of the following reactions.

- One type of serious reaction, called anaphylaxis, may occur soon after getting an antibody. It includes difficulty breathing possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face.
- A second type of serious reaction, called serum sickness, may occur several days to 3 weeks after getting an antibody. It includes hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath.

Rarely, antibodies licensed for treatment of other diseases have been linked to a blood disorder that interferes with blood clotting, to cancer, to damage to the heart muscle, and to the body's immune system attacking healthy cells.

These rare side effects and reactions have not been seen in other studies with the VRC01 antibody.

When antibodies are given to a person by IV they do not last in the body more than a few months. Any antibody given to you in this study should be gone from your body several months after your last dose.

Joining the study

4. It is completely up to you whether or not to join the study.

Take your time in deciding. If it helps, talk to people you trust, such as your doctor, friends or family. If you decide not to join this study, or if you leave it after you have joined, your other care at this clinic and the benefits or rights you would normally have will not be affected.

If you join this study, you may not be allowed to join some other kinds of HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Also during the study, you should not donate blood or tissue.

If you choose not to join this study, you may be able to join another study.

Site: Remove item 5 if you use a separate screening consent that covers these procedures.

5. If you want to join the study, we will screen you to see if you are eligible.

Screening involves a physical exam, HIV test and health history. A physical exam may include, but is not limited to:

- Checking your weight, temperature and blood pressure
- Looking in your mouth and throat
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV. If you could become pregnant, we will test you for pregnancy. If you have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

We will review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

(Sites: adapt the following section so it is applicable to the care available at your site)

6. If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free.

For the care that we cannot give, we will explain how we will help you get care elsewhere.

For health problems that are unrelated to the study, we will not pay for care.

7. If you could become pregnant, you must agree to use birth control to join this study.

Site: If you want to include Appendix B, Approved birth control methods (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the antibody could affect the developing baby. You must agree to use effective birth control from 21 days before you first receive the antibody until your last scheduled clinic visit (about 1¾ years after your first IV). We will talk to you

about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

If you meet the study requirements and want to join, here is what will happen:

8. You will come to the clinic for scheduled visits about [#] times over about 2 years.

The study will require [#] visits. That is 1 visit every 4 weeks for about the first 1½ years and then about every 2 months after that. You may have to come for more visits if you have a lab or health issue.

Visits can last from about [#] minutes to [#] hours. The IV procedure can take about 15 minutes to an hour.

We may contact you after the main study ends (for example, to tell you about the study results).

9. We will give you [Site: Insert compensation] for each study visit you complete.

This amount is to cover the costs of [Site: Insert text]

Site: Insert any costs to participants (eg, birth control costs for participants who could become pregnant).

You do not have to pay anything to be in this study.

10. We will give you either the antibody or a placebo.

Not everyone in this study will get the VRC01 antibody. Some people will get a placebo, a liquid that does not contain any antibody. We will compare the results from people who got the placebo with results from people who got the VRC01 antibody. In this study, the placebo is sterile salt water, which is found naturally in the body.

There are three groups in this study. One group will get a lower dose of the VRC01 antibody, one group will get a higher dose, and one group will get the placebo. The high and low doses of the antibody will be adjusted for your body weight. We will weigh you to determine the amount you will get.

Overall, if you join this study, you have a 2-in-3 chance of getting the study antibody.

Site: Modify the randomization metaphor in the next sentence as appropriate to your local culture.

Whether you get the low dose of the antibody, the high dose of the antibody, or the placebo is completely random, like flipping a coin.

We have no say in whether you get the antibody or the placebo. If you get the antibody, we have no say in which dose you get. We will not know what you are getting, and neither will you. Only the pharmacist at this clinic will have this information while the study is going on.

You will have to wait until everyone completes their final study visits to find out whether you got the antibody or the placebo. This could be up to about 5 years. But, if you have a serious medical problem and need to know what you got before the end of the study, we can tell you.

If it is found to be effective, there are no plans to give the antibody to participants after the study. Instead, we will use what is learned in this study to determine if the antibody would be useful to prevent HIV, how the antibody could be improved, and how to produce it for wide public use.

11. We will give you the antibody or placebo on a schedule.

You will get the VRC01 antibody or the placebo during the study by IV, also known as a drip. To get an IV, a needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small bag of fluid that contains the antibody or placebo. An IV pump controls how fast the fluid drips from the bag, through the tube, and into your vein. There will be 10 IV procedures, one IV every 8 weeks. Other study visits will not include IVs.

Infusion schedule

Group	Dose	First IV	Weeks after first IV								
			Wk 8	Wk 16	Wk 24	Wk 32	Wk 40	Wk 48	Wk 56	Wk 64	Wk 72
Group 1	Lower dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 2	Higher dose VRC01	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Group 3	Placebo	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

You will have to wait in the clinic for about 30 minutes after the first IV to see if there are any problems. You probably will not have to wait after the IVs at the rest of the IV visits. After each IV visit, for that night and for three more days, you will be asked to keep track of how you feel. To help you do this, we can give you tools and show you how to use them. We will ask you the ways we can contact you. We will contact you about 3 days after each IV visit to ask how you have been feeling. Contact the clinic staff if you have any concerns after getting an infusion. If you have a problem, we will continue to check on you until it goes away.

12. In addition to giving you the antibody or placebo, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you could become pregnant;
- Ask questions about your health, including medications you may be taking;
- Ask questions about any personal problems or benefits you may have from being in the study; and
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 30 mL and 180 mL (6 teaspoons to $\frac{3}{4}$ cup). Your body will make new blood to replace the blood we take out.

Site: You may want to add a sentence to the end of the previous paragraph contextualizing the blood volumes described (eg, “To compare, people who donate blood in the US can give a total of about 500 mL in an 8-week period.”). Modify the example for cultural relevance and alter blood volumes as necessary.

*Site: Insert the **first** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.*

We will be looking for side effects.

About every six months we will do a blood test for syphilis and will test your urine or a cervical/vaginal swab for gonorrhea and chlamydia. At these times we will also test you for Trichomonas using a cervical/vaginal swab. We will explain what each of these infections is. If the tests show that you have an infection, we will provide counseling and will help you get treatment. This study cannot pay for that treatment. *[Site: Revise preceding sentence if you provide or pay for STI treatment.]*

We will review the results of the procedures and tests with you at your next visit, or sooner if necessary. If any of the results are important to your health, we will tell you.

13. We will test your samples for this study.

We will send your samples (without your name) to labs approved by the HVTN and the HPTN for this study. These labs are located in the United States and South Africa. The samples will be tested to:

- measure how much antibody is in your blood,
- see how your immune system responds to the antibody, and
- see if there is antiretroviral medicine (also called ART/ARV) in your blood.

Researchers may also do genetic testing related to this study on your samples. Your genes are passed to you from your birth parents. They affect how you look and how your body works. The differences in people's genes can help explain why some people get a disease while others do not. These types of genetic tests involve only some of your genes, not all of your genes (your genome). The researchers will study the genes related to the immune system and HIV and those that affect how people get HIV.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the antibody.

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

Tests done on your samples are for research purposes only. The labs will not give the results to you or this clinic, and the results will not become part of your study record.

When your samples are no longer needed for this study, the HVTN will continue to store them.

Site: Delete next section if using separate consent for use of samples and information in other studies

14. When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these "extra samples."

This section gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

Do I have to agree? No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

Where are the samples stored? Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in South Africa.

How long will the samples be stored? There is no limit on how long your extra samples will be stored. [Site: insert limits if your regulatory authority imposes them.]

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

Will I benefit from allowing my samples to be used in other studies? Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

Will the HVTN or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

How do other researchers get my samples and information? When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

What information is shared with other researchers? The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

What kind of studies might be done with my extra samples and information? The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- Any regulatory agency that reviews clinical trials
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

15. We will counsel you on reducing your risk for HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior and drug use. We will provide you with condoms and lubricant. We will talk with you about ways of lowering your risk of getting HIV. We will help you develop a risk reduction plan. Some topics we may discuss include:

- What you think causes risky behavior for you, and
- Ways to avoid getting HIV or giving it to someone else

[Site: Adjust the language in this paragraph about PrEP provision to meet local availability. The current text reflects the situation in the Republic of South Africa.] These methods may include not having sex, using condoms, or other behavior changes. We will talk about new methods of HIV prevention as they become available. These methods may include the use of anti-HIV drugs taken every day to prevent HIV. This is called pre-exposure prophylaxis or PrEP. In the

past few months a combination of two anti-HIV drugs (TDF/FTC) has been licensed in South Africa and Kenya for use to prevent HIV infection in people at high risk. Studies in women have shown this drug combination can reduce the risk of getting HIV when it is taken every day. The drug combination is not always effective and HIV infections may happen, especially if the medicine is not taken every day. This drug combination is available in the private health sector by prescription from a doctor. The Ministry of Health in South Africa is starting several programs called “demonstration projects” that provide this drug combination to people free of charge. We can refer you to the nearest of these programs if you are interested.

In this study, we will look at how many participants use PrEP. We will also try to find out if using PrEP has any effect on how VRC01 works.

[Site: If you prefer to use Appendix E, Sample consent form for participants with HIV infection at enrollment or during the study, include the following section and delete the two succeeding sections that are highlighted in green. If you prefer not to use Appendix E, delete the following section and INCLUDE the two sections highlighted in green.]

16. If you are HIV infected when you enroll or become infected during the study, we will help you get care and support.

We will test your blood for HIV before your first IV and during the study. Each time, it will take a few days to complete the tests. If you are infected with HIV, you cannot stay in the study for its whole length. If that happens, we will tell you as soon as possible. We will also ask you to come to the clinic for 2-5 more visits. We will tell you more about what will happen at these visits in another form.

17. If you are found to have been HIV-1 infected when you enrolled, or if you have HIV-2 infection:

If you are found to have been HIV infected when you enrolled, you were already infected with HIV before you got the antibody or placebo. It takes a few days to complete the tests to see if you have HIV, so your infection was not found until after you got your first IV.

HIV-2 is a rare kind of HIV, most often found in West Africa.

We will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s).

We will ask you to come to the clinic for 2 more visits within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;

- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 30 and 45 mL, or about 2 to 3 tablespoons, at each visit); and
- Do pregnancy tests if you could become pregnant;
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **second** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

18. If you got infected with HIV-1 during the study:

If you became infected with HIV-1, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). You will not get any more IVs. We will ask you to come in for 5 more visits within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 70 mL and 130 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **third** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

19. If you stop getting IVs for reasons other than HIV infection, we may encourage you to stay in the study.

We will ask you to come in for study visits about every 3-4 months until 104 weeks (2 years) after your first infusion. That is how long you would be in the

study if you got all the infusions on schedule. Because you got some IVs, we want to keep track of your health. How many visits you will have will depend on when you stopped getting IVs. At these visits we will:

Ask questions about your health, including medications you may be taking;

- Do physical exams based on your complaints or side effects;
- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Ask questions about any personal problems or benefits you may have from participating in the study;
- Do pregnancy tests if you could become pregnant;
- Collect urine samples; and
- Collect blood samples (between 70 mL and 120 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit).

*[Site: Insert the **last** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

20. We may stop your IVs and take you out of the study at any time. We may do this even if you want to stay in the study and even if you were scheduled for more IVs.

This may happen if:

- we learn that you were enrolled in the study in error,
- you are unable to follow instructions,
- we think that staying in the study might harm you,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

If we take you out of the study, we will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study.

21. We will stop your IVs if you become pregnant during the study.

We will encourage you to stay in the study if you choose. We will discuss your study options with you. If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

22. We will do our best to protect your private information.

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary. We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

Clinic staff will have access to your study records. Your records may also be reviewed by groups who watch over this study to see that we are protecting your rights, keeping you safe, and following the study plan. These groups include:

- The US National Institutes of Health, people who work for them, its study monitors, and its chosen South African representatives,
- The US Food and Drug Administration,
- Any regulatory agency that reviews clinical trials
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The HVTN and HPTN and people who work for them,
- The US National Institutes for Allergy and Infectious Diseases Data and Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

We cannot guarantee absolute privacy. At this clinic, we have to report the following information:

Site: Include any public health or legal reporting requirements. Bulleted examples should include all appropriate cases (reportable communicable disease, risk of harm to self or others, etc.).

- [Item 1]

- [Item 2]
- [Item 3]

The results of this study may be published. No publication will use your name or identify you personally.

We may share information from the study with other researchers. We will not share your name or information that can identify you.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Other Risks

23. There are other risks to being in this study.

This section describes the other risks and restrictions we know about. There may also be unknown risks, even serious ones. We will tell you if we learn anything new that may affect your willingness to stay in the study.

Risks of taking blood:

Taking blood can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of the IV procedures:

Getting an IV may cause stinging, discomfort, pain, soreness, redness, bruising, itching, rash, and swelling where the needle goes into the skin. Rarely, needle sticks can result in infections.

Personal problems/discrimination:

Some people who join HVTN or HPTN studies report personal problems or discrimination because of joining an HIV prevention study. Family or friends may worry, get upset or angry, or assume that you are infected with HIV or at high risk and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

HIV testing

HIV antibody tests are the usual way to test for HIV infections. Although 2 out of 3 people in this study will get an HIV antibody, we do not expect them to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the VRC01 antibody and none of them detected the antibody.

Although it has not been seen so far, getting VRC01 may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

To be absolutely safe we ask you to get HIV tests only at this clinic during the study. Our tests can always detect true HIV infection. They can also tell if someone is really not HIV infected. Since the antibodies do not last long in the body, we do not expect you to have any problems with HIV testing after the study ends.

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you are infected with HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

Risks of genetic testing:

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

Unknown risks:

We do not know if the antibody will increase, decrease, or not change your risk of becoming infected with HIV if exposed.

If we find that you were already HIV infected when you got the antibody, we do not know how the antibody will affect your HIV disease. We also do not know how having gotten it will affect your HIV-related lab results.

If you get infected with HIV during the study, we do not know how the antibody might affect the course of your HIV disease.

If you become pregnant while you still have VRC01 in your body, we don't know if it could be passed to your baby. We do not know how the antibody will affect a pregnant participant or a developing baby.

Benefits

24. The study may not benefit you.

Since we do not know if the antibody can prevent HIV infection in people, you should not expect any benefit from getting the antibody in this study. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

This study may show us that the VRC01 antibody can prevent HIV and the study results may also help in the search for methods to prevent HIV. However, if the VRC01 antibody later becomes approved and sold or leads to an HIV prevention method, there are no plans to share any money with you.

Your rights and responsibilities

25. If you join the study, you have rights and responsibilities.

You have many rights that we will respect. You also have responsibilities. We list these in the Participant's Bill of Rights and Responsibilities. We will give you a copy of it.

Leaving the study

26. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

If you decide to leave the study, we will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Injuries

Sites: Do not make changes to the following section without obtaining approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org.

27. If you get sick or injured during the study, contact us immediately.

Your health is important to us. *(Sites: adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will explain how we will help you get care elsewhere.

If you become sick or injured in this study, there is a process to decide if it is related to the VRC01 antibody and/or study procedures. If it is, we call it a study-related injury.

Next paragraph for all sites except in Zimbabwe.

(Sites: adjust the language in this paragraph so it is applicable to your site. Note: Insurance is purchased for all African countries except Zimbabwe. The ABPI guidelines may only apply to South Africa and Mozambique.)

In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury. The insurance will follow the Association of the British Pharmaceutical Industry guidelines for payment of study-related injury. We can give you a copy of these guidelines. In rare cases, the insurance funds may not be enough. If needed, the HVTN and HPTN have limited funds to pay medical costs for study-related injuries that they determine are reasonable. *(Sites: insert locale-appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV prevention study. Or you might lose wages because you cannot go to work. However, there are no funds to pay for these kinds of injuries, even if they are study related.

You may disagree with the decision about whether your injury is study related. If you wish, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

28. If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact
[name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

South African sites: Include the following:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 9201

e-mail: gouwsj@health.gov.za

Your permissions and signature

Site: Delete this section if using a separate consent for use of samples and information in other studies.

29. In Section 14 of this form, we told you about possible other uses of your extra samples and limited information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

30. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix B Approved birth control methods (for sample informed consent form)

You should not become pregnant during the study because we do not know how the study antibody could affect the developing baby.

If you were born female and are sexually active in a way that could lead you to get pregnant, you must agree to use effective birth control from 21 days before your first IV until your last scheduled clinic visit (about 2 years after your first IV). You should not become pregnant during the study because we do not know how the antibody could affect the developing baby.

Effective birth control means using any of the following methods:

- Birth control drugs that prevent pregnancy—given by pills, patches, vaginal rings, injectables, or implant under the skin; or
- Intrauterine device (IUD).

You do not have to use birth control if:

- You have been diagnosed with early menopause, with no menstrual periods for one year;
- You have had a hysterectomy (your uterus removed);
- You have had your ovaries removed;
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes.

Remember: If you are having sex, you need to use male or female condoms to protect yourself from HIV infection.

If you join the study, we will test you for pregnancy at some visits, including before each study IV.

Appendix C Sample consent form for use of samples and information in other studies

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

HVTN protocol number: HVTN 703/HPTN 081, The AMP Study

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to keep them for use in other studies by HVTN, HPTN, or other researchers. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. At your request, we will destroy all extra samples that we have. Your decision will not affect your being in this study or have any negative consequences here.

2. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. Your samples will be stored in the HVTN repository in South Africa.

3. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. *[Site: insert limits if your regulatory authority imposes them.]*

4. Will I be paid for the use of my samples?

No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we will not be able to get them back.

7. How do other researchers get my samples and information?

When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN and HPTN will send your samples to the researcher's location.

8. What information is shared with other researchers?

The samples and limited information will be labeled with a code number. Your name will not be part of the information. However, some information that we share may be personal, such as your race, ethnicity, gender, health information from the study, and HIV status. We may share information about the study product you received and how your body responded to the study product.

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV prevention or infection, the immune system, and other diseases.

Researchers may also do genetic testing on your samples.

If you become HIV infected, the researchers may look at all of the genes of the virus found in your samples. The researchers will use this information to learn more about HIV and the study product(s).

In some cases, researchers may take cells from your samples and grow more of them over time, so that they can continue to contribute to this study.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

The genetic testing could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

11. Who will have access to my information in studies using my extra samples?

People who may see your information are:

- Researchers who use your stored samples and limited information for other research
- Government agencies that fund or monitor the research using your samples or information
- Any regulatory agency that reviews clinical trials
- The researcher's Institutional Review Board or Ethics Committee
- The people who work with the researcher

All of these people will do their best to protect your information. The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact [name and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact [name/title/phone of person on IRB or other appropriate organization].

South African sites: Include the following:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not

provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 9201

e-mail: mogobm@health.gov.za

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN and HPTN keep track of your decision about how your samples and information can be used.

☐

I allow my extra samples combined with limited information to be used for other studies related to HIV prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐

I agree to the option above and also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐

I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)

Witness's signature

Date

Time

*Witness is impartial and was present for the consent process.

Appendix D Tables of procedures (for sample informed consent form)

[Site: You may insert these tables of procedures into appropriate sections of your consent form(s) or give them to study volunteers/participants separately if you think they would be helpful. You are not required to do either.]

HIV-uninfected participants

	6 months 1 year 1½ years 2 years																											
	Screening visit(s)	First IV visit	4 weeks	8 weeks	8 weeks + 5 days	12 weeks	16 weeks	20 weeks	24 weeks	28 weeks	32 weeks	36 weeks	40 weeks	44 weeks	48 weeks	52 weeks	56 weeks	60 weeks	64 weeks	68 weeks	72 weeks	76 weeks	80 weeks	88 weeks	96 weeks	104 weeks		
Procedure																												
IV		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓							
Medical history	✓																											
Complete physical exam	✓																									✓		
Brief physical exam		✓		✓			✓		✓		✓		✓		✓		✓		✓		✓							
Urine test	✓			✓																			✓					
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Pregnancy test*	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓		✓					
HIV test & pretest counseling	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Risk reduction counseling	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					✓		
Interview/Questionnaire	✓	✓		✓			✓		✓		✓		✓		✓		✓		✓		✓					✓		
STI testing (blood, urine, and/or swabs) [†]		✓							✓						✓					✓								

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

[†] And if clinically indicated.

Participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Weeks after 1 st positive HIV test	
	4	24
Medical history (as needed)	✓	✓
Brief physical (as needed)	✓	✓
Complete physical		✓
Risk reduction counseling	✓	✓
Questions/questionnaire	✓	✓
Blood drawn	✓	✓

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected

Procedure	Weeks after 1 st positive HIV test				
	4	6	8	12	24
Medical history (as needed)	✓	✓	✓	✓	✓
Brief physical (as needed)	✓	✓	✓	✓	
Complete physical					✓
Risk reduction counseling	✓	✓	✓	✓	✓
Questions/questionnaire	✓	✓	✓	✓	✓
Blood drawn	✓	✓	✓	✓	✓
Pregnancy test*				✓	

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

Participants who become HIV-1–infected may be invited to join a separate study for follow-up visits. That study will have a separate schedule of visits and procedures. It will also have a separate consent form, which will be reviewed with all participants who are invited to join that study.

* Persons who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Participants who discontinue infusions for reasons other than HIV infection

Procedure	Weeks after enrollment							
	8	20	32	44	56	72	88	104
Brief physical (as needed)	√	√	√	√	√	√	√	
Complete physical								√
HIV testing & pretest counseling	√	√	√	√	√	√	√	√
Risk reduction counseling	√	√	√	√	√	√	√	√
Questions/questionnaire	√	√	√	√	√	√	√	√
Urine test	√						√	
Pregnancy test*	√		√		√		√	
Blood drawn	√	√	√	√	√	√	√	√

Study participants who discontinue infusions for reasons other than HIV infection will start this visit schedule at the first visit that occurs after their last infusion.

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out whether you received the study antibody or the placebo.

* Persons who have had their uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, are not required to have pregnancy tests.

Appendix E Sample consent form for participants with HIV infection at enrollment or during the study

Title: A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

Protocol number: HVTN 703/HPTN 081, The AMP Study

Site: [Insert site name]

Please read this consent form or ask someone to read it to you. If you decide to, we will ask you to sign or make your mark on this form. We will offer you a copy to keep. We will ask you questions to see if we have explained everything clearly. You can also ask us questions about the study.

You are a participant in a study called HVTN 703/HPTN 081, The AMP Study. The rest of the information in the consent form that you signed earlier, about the study purpose, the risks and benefits of participation, your rights and responsibilities, and how your privacy is protected, continues to be important information for you and has not changed.

About this form

We tested your blood for HIV and you were found to be infected. We will help you get care and support.

You became infected either prior to enrollment or during your participation in the study. Because of this, you cannot stay in the study for its whole length. We would like you to come to the clinic for a different number of visits than what is explained in the main study consent form.

Depending on when you became infected, you will come to the clinic for 1-5 more visits, including today.

1. If you are found to have been HIV-1 infected when you enrolled, or if you have HIV-2 infection:

If you are found to have been HIV infected when you enrolled, you were already infected with HIV before you got the antibody or placebo. It takes a few days to complete the tests to see if you have HIV, so your infection was not found until after you got your first IV.

HIV-2 is a rare kind of HIV, most often found in West Africa.

We will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s).

We are asking you to come to the clinic for 1-2 more visits (including today) within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 30 and 45 mL, or about 2 to 3 tablespoons, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **second** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

2. If you got infected with HIV-1 during the study:

If you became infected with HIV-1, we will counsel you about your HIV infection, talk with you about ways to avoid transmission and about telling your partner(s). You will not get any more IVs. We will ask you to come in for 4-5 more visits (including today) within about 6 months of your diagnosis. At these visits, we will:

- Ask questions about your health;
- Do physical exams based on your complaints or symptoms;
- Ask questions about your risk of infecting others with HIV, including sexual behavior and drug use;
- Counsel you on ways to avoid transmitting HIV to other people;
- Collect blood samples (between 70 mL and 130 mL, about $\frac{1}{3}$ to $\frac{1}{2}$ cup, at each visit); and
- Ask questions about any personal problems or benefits you may have from participating in the study.

*[Site: Insert the **third** table in Appendix D, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.]*

Leaving the study

3. Tell us if you decide to leave the study.

You are free to leave the study at any time and for any reason. Your care at this clinic and your legal rights will not be affected, but it is important for you to let us know.

We will ask you to come back to the clinic one last time for a physical exam, and we may ask to take some blood and urine samples. We will also ask about any personal problems or benefits you have experienced from being in the study. We believe these steps are important to protecting your health, but it is up to you whether to complete them.

Questions

If you have questions or problems at any time during your participation in this study, use the following important contacts.

If you have questions about this study, contact [name and telephone number of the investigator or other study staff].

If you have any symptoms that you think may be related to this study, contact [name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact [name/title/phone of person on IRB or other appropriate organization].

If you want to leave this study, contact [name and telephone number of the investigator or other study staff].

South African sites: Include the following:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Medicines Control Council (MCC) at:

The Registrar of Medicines
Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001

Fax: (012) 395 9201

e-mail: mogobm@health.gov.za

Your permissions and signature

If you agree to continue in this study with this new visit schedule, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand the changes to the visit schedule and what will happen to you. You understand that the possible risks and benefits of participation have not changed.
- You have had your questions answered and know that you can ask more at any time.
- You agree to continue in this study.

You will not be giving up any of your rights by signing this consent form.

_____	_____	_____	_____
Participant's name (print)	Participant's signature or mark	Date	Time

_____	_____	_____	_____
Study staff conducting consent discussion (print)	Study staff signature	Date	Time

For participants who are unable to read or write, also complete the signature block below:

_____	_____	_____	_____
Witness's name (print) [#]	Witness's signature	Date	Time

[#] Witness is impartial and was present for the consent process.

Appendix F Schedule 1—Laboratory procedures for HIV-uninfected participants

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ⁴	Tube size (vol. capacity) ⁴	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Total
					Day:	Screening visit ³	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D616	D672	D728	
					Week:		W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W88	W96	W104	
						Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10							
BLOOD COLLECTION																																
Screening/Diagnostic																																
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics ⁷	HSML-NICD / UW-VSL	HSML-NICD / UW-VSL	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	20 ⁷	260
Safety labs																																
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	55
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	5	—	5	—	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	5	—	—	—	—	55
STI Serology																																
Syphilis ¹¹	Local lab	Local lab	SST	5mL	—	5 ¹³	—	—	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	5 ¹³	—	—	—	—	—	20
Drug Levels/Detection																																
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0
ARV detection by serum or plasma ¹⁰	CSR	JHU	SST	8.5mL	—	y	—	y	—	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	y	—	—	0
ARV detection by dried blood spots ¹⁶	CSR	HVTN Labs	EDTA	2mL	—	See footnote 16																									0	
Immunogenicity & Virologic Assays																																
Host genetics ⁵	CSR	HVTN Labs	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Anti-VRC01 Ab levels	CSR	VRC/NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	y	—	—	—	—	—	—	—	—	—	—	y	—	—	—	—	0
Functional humoral assays ⁸	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0
Viral isolation/sequencing ⁹	CSR	HVTN Labs	EDTA	10mL	—	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	250
STORAGE																																
Serum storage	CSR	—	SST	8.5mL	—	76.5	51	51	42.5	51	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	51	42.5	42.5	42.5	1139	
PBMC storage	CSR	—	ACD	8.5mL	—	51	—	—	—	—	—	—	—	—	—	34	—	—	—	—	—	—	—	—	—	34	—	—	—	34	153	
Visit total ¹⁷					15	165	73	83	65	73	75	65	80	65	75	73	109	65	80	65	75	65	75	65	114	73	65	65	65	109	1987	
56-Day total ¹⁷					15	180	253	336	221	294	295	212	219	209	219	212	256	246	253	209	219	204	214	204	253	251	251	129	129	173		
URINE COLLECTION																																
Urine dipstick ¹⁵	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	
Pregnancy Test ⁶	Local lab	Local lab			X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	
CERVICAL/VAGINAL SWAB COLLECTION																																
Trichomonas vaginalis	Local lab	Local lab			—	X ¹⁴	—	—	—	—	—	—	—	X ¹⁴	—	—	—	—	—	X ¹⁴	—	—	—	—	—	X ¹⁴	—	—	—	—	—	
EITHER URINE OR CERVICAL/VAGINAL SWAB COLLECTION																																
Urine - Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	
Cervical/Vaginal Swab - Chlamydia/Gonorrhea ¹²	Local lab	Local lab			—	X ¹³	—	—	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	X ¹³	—	—	—	—	—	

¹ CSR = central specimen repository; HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa); UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA)

² HVTN Laboratories include: Cape Town HVTN Immunology Laboratory (CHIL, Cape Town, South Africa); South African Immunology Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa); University of Colorado Denver (Aurora, Colorado, USA).
Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA); JHU = Johns Hopkins University, HPTN Laboratory Center (Baltimore, Maryland, USA).

³ Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

⁴ Local labs may assign appropriate alternative tube types for locally performed tests.

⁵ Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

- ⁶ Pregnancy test must be performed on urine or blood specimens on the day of infusion with negative results received prior to infusion.
- ⁷ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 26 above.
- ⁸ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.
- ⁹ EDTA blood collected for plasma may also be used for ARV detection assay, if necessary.
- ¹⁰ Testing plan for ARV detection to be determined.
- ¹¹ Syphilis testing will be done by serology.
- ¹² Chlamydia/Gonorrhea testing will be done with **EITHER urine OR cervical/vaginal swab**. Either specimen is acceptable, and clinics will determine which specimen will be collected and tested.
- ¹³ Syphilis testing, and chlamydia/gonorrhea testing by either urine or cervical/vaginal swab, will be performed at visits 2, 9, 15, and 21; in addition, testing may occur at any visit if clinically indicated.
- ¹⁴ Cervical/vaginal swab will be collected for Trichomonas testing at visits 2, 9, 15, and 21; in addition, testing may occur at any visit if clinically indicated.
- ¹⁵ And microscopy if needed.
- ¹⁶ EDTA blood for dried blood spots will be collected on regularly scheduled calendar days throughout the study. Refer to the Specimen Collection SSP for more information.
- ¹⁷ The total 56-day blood collection includes 2mL EDTA blood collection for dried blood spots. It is highly improbable that the 2mL EDTA blood collection will occur at every possible timepoint, but it is reflected in the blood draw totals for every visit to account for this extreme possibility.
- y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, ARV detection, and functional humoral assays; no separate blood draw is needed.
- z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

Appendix G Schedule 2—Laboratory procedures for HIV-1–infected participants

						Visit:	#.X ⁵						
						Visit:	31	32	33	34	35		
						Days:	D28	D42	D56	D84	D168		
						Weeks after diagnosis ⁷ :	W4	W6	W8	W12	W24		
Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³								Total	
BLOOD COLLECTION													
Screening or diagnostic assays													
HIV diagnostics	HSML-NICD / UW-VSL	HSML-NICD / UW-VSL	EDTA	10mL	20		—	—	—	—	—	20	
HIV PCR viral load	HSML-NICD	HSML-NICD	EDTA	10mL	—		10	10	10	10	10	50	
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5		5	5	5	5	5	30	
Safety lab													
Hemoglobin	Local Lab	Local Lab	EDTA	5mL	—		—	—	5	5	—	10	
Drug levels													
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5		8.5	8.5	8.5	8.5	8.5	51	
Immunogenicity & Virologic Assays													
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17		17	17	17	17	17	102	
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10		10	10	10	10	10	60	
Storage													
Serum	CSR		SST	8.5mL	25.5		17	17	17	17	17	110.5	
Plasma	CSR		EDTA	5mL	5		5	5	5	5	5	30	
PBMC	CSR		ACD	8.5mL	34		—	—	—	34	34	102	
Visit total					125		72.5	72.5	77.5	111.5	106.5	566	
56-Day total					125		198	270	348	334	106.5		
URINE COLLECTION													
Pregnancy Test ⁴	Local Lab	Local Lab			X		—	—	—	X	—		

¹ CSR = central specimen repository; HSML-NICD = HIV Sero-Molecular Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa); UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA)

² HVTN Laboratories include: South African Immunology Laboratory-National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa)

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA)

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ Pregnancy test may be performed on blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

Appendix H Schedule 3—Laboratory procedures for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³	Visit: #.X ⁵	Visit: 47 48		Total	
						Days: D28	D168		
						Weeks after diagnosis ⁷ : W4	W24		
BLOOD COLLECTION									
Screening or diagnostic assays									
HIV diagnostics	HSML-NICD / UW-VSL	HSML-NICD / UW-VSL	EDTA	10mL	20		—	—	20
HIV PCR viral load	HSML-NICD	HSML-NICD	EDTA	10mL	—		10	10	20
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	5		5	5	15
Drug levels									
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	8.5		—	—	8.5
Immunogenicity & Virologic Assays									
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	17		—	—	17
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10		—	—	10
Storage									
Serum	CSR		SST	8.5mL	25.5		17	17	59.5
Plasma	CSR		EDTA	5mL	5		—	—	5
PBMC	CSR		ACD	8.5mL	34		—	—	34
Visit total					125		32	32	189
56-Day total					125		157	32	
URINE COLLECTION									
Pregnancy Test ⁴	Local Lab	Local Lab			X		—	—	

¹ CSR = central specimen repository; HSML-NICD = HIV Sero-Molecular Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa); UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

² HVTN Laboratories include: South African Immunology Laboratory–National Institute for Communicable Diseases (SAIL-NICD, Johannesburg, South Africa); Duke University Medical Center (Durham, North Carolina, USA) ; University of Cape Town (Cape Town, South Africa).

Non-HVTN laboratories: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ Pregnancy test may be performed on blood specimens.

⁵ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit, in addition to the other indicated specimens. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple subsequent Redraw visits may be necessary; only the EDTA blood specimens for HIV diagnostics, viral isolation/sequencing, and plasma storage will be collected at the subsequent Redraw visits. Refer to the HIV Testing SSP for more information.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request.

Appendix I Schedule 4—Laboratory procedures for participants who discontinue infusions for reasons other than HIV infection

					Visit:	71	72	73	74	75	76	77	78	Total
					Days after enrollment:	D56	D140	D224	D308	D392	D504	D616	D728	
					Weeks after enrollment:	W8	W20	W32	W44	W56	W72	W88	W104	
Procedure	Ship to ¹	Assay location ^{1,2}	Tube Type ³	Tube size (vol. capacity) ³										
BLOOD COLLECTION														
Screening or diagnostic assays														
HIV diagnostics ⁵	HSML-NICD / UW-VSL	HSML-NICD / UW-VSL	EDTA	10mL	10	10	10	10	10	10	10	10	20 ⁵	90
Safety labs														
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	—	5	—	5	—	—	—	—	15
ALT, Creatinine	Local lab	Local lab	SST	5mL	5	—	5	—	5	—	—	—	—	15
Drug Levels														
VRC01 Ab levels	CSR	NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	y	0
Immunogenicity & Virologic Assays														
Functional humoral assays ⁶	CSR	HVTN Labs / VRC / NVITAL	SST	8.5mL	y	y	y	y	y	y	y	y	y	0
Viral isolation/sequencing	CSR	HVTN Labs	EDTA	10mL	10	10	10	10	10	10	10	10	10	80
STORAGE														
Serum storage	CSR	—	SST	8.5mL	51	42.5	42.5	42.5	42.5	42.5	42.5	42.5	42.5	349
PBMC storage	CSR	—	ACD	8.5mL	—	—	—	—	—	—	—	—	34	34
Visit total					81	63	73	63	73	63	63	63	107	583
56-Day total					81	63	73	63	73	63	63	63	107	
URINE COLLECTION														
Urine dipstick ⁷	Local lab	Local lab			X	—	—	—	—	—	—	X	—	
Pregnancy Test ⁴	Local lab	Local lab			X	—	X	—	X	—	—	X	—	

¹ CSR = central specimen repository; HSML-NICD = HIV Sero-Molecular Laboratory-National Institute for Communicable Diseases (Johannesburg, South Africa) ; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA)

² HVTN Laboratories include: South African Immunology, Laboratory-National Institute for Communicable Diseases (SAIL-NICD Johannesburg, South Africa); Duke = Duke University Medical Center (Durham, North Carolina, USA); University of Cape Town (Cape Town, South Africa)

Non-HVTN laboratory: NVITAL = NIAID Vaccine Immune T-Cell Antibody Laboratory (Gaithersburg, Maryland, USA); VRC = Vaccine Research Center (Bethesda, Maryland, USA).

³ Local labs may assign appropriate alternative tube types for locally performed tests.

⁴ Pregnancy test may be performed on blood specimens.

⁵ At an early termination visit for a withdrawn or terminated participant (see Section 7.12), blood should be drawn for HIV diagnostic testing, as shown for visit 78 above.

⁶ Functional humoral assays include nAb, ADCC, virion capture, and phagocytosis assays.

⁷ And microscopy if needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level and functional humoral assays; no separate blood draw is needed.

Appendix J Schedule 1—Procedures at CRS for HIV-uninfected participants

	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	Post
	Day:	Screening	D0	D28	D56	D61	D84	D112	D140	D168	D196	D224	D252	D280	D308	D336	D364	D392	D420	D448	D476	D504	D532	D560	D616	D672	D728	
	Week:	visit ¹	W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W88	W96	W104	
	Procedure	Scr.	Inf#1		Inf#2			Inf#3		Inf#4		Inf#5		Inf#6		Inf#7		Inf#8		Inf#9		Inf#10						
Study procedures ²																												
Signed screening consent (if used)		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Risk reduction counseling		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Pregnancy prevention assessment ³		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Confirm eligibility, obtain demographics, randomize		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Participant Questionnaire		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Concomitant medications		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
Intercurrent illness/adverse experience		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	X	—
HIV infection assessment ⁴		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant ¹³		—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local lab assessment																												
Screening HIV test		X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Urine dipstick ¹²		X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Pregnancy (urine or serum HCG) ⁵		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—
CBC, differential		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
ALT, Creatinine		X	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Syphilis ⁶		—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—
Chlamydia, Gonorrhea ⁸		—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—	X ⁷	—	—	—	—	—	—	X ⁷	—	—	—	—	—
Trichomonas vaginalis (cervical/vaginal swab)		—	X ⁹	—	—	—	—	—	—	X ⁹	—	—	—	—	—	X ⁹	—	—	—	—	—	—	X ⁹	—	—	—	—	—
Study product administration procedures																												
IV infusion ¹⁰		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Reactogenicity assessment ¹¹		—	X	—	X	—	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	X	—	—	—	—	—	—
Poststudy																												
Unblind participant		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X

Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

² For specimen collection requirements, see [Appendix F](#).

³ Pregnancy prevention assessments are required only for participants who are capable of becoming pregnant.

⁴ Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

- ⁵ Pregnancy test must be performed on the day of infusion with negative results received prior to infusion. Pregnancy test to determine eligibility may be performed at screening, but must also be done on Day 0 prior to infusion. Persons who are NOT capable of becoming pregnant due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.
- ⁶ Syphilis testing will be done by serology.
- ⁷ Syphilis and Chlamydia/Gonorrhea testing may be performed at additional timepoints if clinically indicated.
- ⁸ Chlamydia/Gonorrhea testing will be done by urine or cervical/vaginal swab.
- ⁹ Cervical/vaginal swab may be collected for Trichomonas testing at additional timepoints if clinically indicated.
- ¹⁰ Blood draws required at infusion visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests must be drawn within the 3 days prior to infusion.
- ¹¹ Reactogenicity assessments performed for 3 days postinfusion (see Section [7.10](#)).
- ¹² And microscopy if needed.
- ¹³ If HIV test results are not available at the visit indicated, provide test results at the next available opportunity.

Appendix K Schedule 2—Procedures at CRS for HIV-1–infected participants

Visit Number:	#.X ¹		31	32	33	34	35
		Days after diagnosis ²	D28	D42	D56	D84	D168
		Weeks after diagnosis	4	6	8	12	24
Study procedures³							
Counseling on HIV-1 testing/diagnosis	X		X	—	—	—	—
Abbreviated physical exam ⁴	X		X	X	X	X	—
Complete physical exam ⁴	—		—	—	—	—	X
ART assessment	X		X	X	X	X	X
Concomitant medications	—		X	X	X	X	X
Intercurrent illness/adverse experience	—		X	X	X	X	X
Transmission risk reduction counseling	X		X	X	X	X	X
Behavioral risk assessment questionnaire	—		—	—	—	—	X
Social impact assessment	X		X	X	X	X	X
Local lab assessment							
Pregnancy test ⁵	X		—	—	—	X	—
CD4+ T cell count	X		X	X	X	X	X
Hemoglobin					X	X	

¹ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple Redraw visits may be necessary; only the blood specimen indicated in [Appendix G](#) will be collected at the subsequent Redraw visits.

² Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request

³ For specimen collection requirements, see [Appendix G](#).

⁴ Includes assessment of HIV/AIDS-related conditions.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix L Schedule 3—Procedures at CRS for participants discovered to have been HIV-1–infected at enrollment or who become HIV-2–infected

Visit Number	#.X ¹		47	48
		Days after diagnosis ²	D28	D168
		Weeks after diagnosis	4	24
Study procedures³				
Counseling on HIV-1 testing/diagnosis	X		X	—
Abbreviated physical exam ⁴	X		X	—
Complete physical exam ⁴	—		—	X
ART assessment	X		X	X
Concomitant medications	—		X	X
Intercurrent illness/adverse experience	—		X	X
Transmission risk reduction counseling	X		X	X
Behavioral risk assessment questionnaire	—		—	X
Social impact assessment	X		X	X
Local lab assessment				
Pregnancy test ⁵	X		—	—
CD4+ T cell count	X		X	X

¹ Visit #.X indicates a Redraw visit where # is a Schedule 1 visit number. Confirmatory draw for HIV diagnostics will be collected at the Redraw visit. The Redraw visit should occur as soon as possible after the clinic receives a Redraw Request from the HIV diagnostics laboratory. Multiple Redraw visits may be necessary; only the blood specimens indicated in [Appendix H](#) will be collected at the subsequent Redraw visits.

² Date of diagnosis = date of the initial specimen draw that led to the first Redraw Request

³ For specimen collection requirements, see [Appendix H](#).

⁴ Includes assessment of HIV/AIDS-related conditions.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix M Schedule 4—Procedures at CRS for participants who discontinue infusions for reasons other than HIV infection

Visit Number:	71	72	73	74	75	76	77	78	Post
Days after enrollment:	56	140	224	308	392	504	616	728	
Weeks after enrollment:	8	20	32	44	56	72	88	104	
Study procedures¹									
Abbreviated physical exam	X	X	X	X	X	X	X	—	—
Complete physical exam	—	—	—	—	—	—	—	X	—
Risk reduction counseling	X	X	X	X	X	X	X	X	—
Concomitant medications	X	X	X	X	X	X	X	X	—
Intercurrent illness/adverse experience	X	X	X	X	X	X	X	X	—
HIV infection assessment ²	X	X	X	X	X	X	X	X	—
Confirm HIV test results provided to participant ³	X	X	X	X	X	X	X	X	X
Behavioral risk assessment questionnaire	—	X	—	X	—	X	—	X	—
Social impact assessment	X	X	X	X	X	X	X	X	—
Local lab assessment									
Urine dipstick ⁴	X	—	—	—	—	—	X	—	—
Pregnancy test ⁵	X	—	X	—	X	—	X	—	—
Poststudy									
Unblind participant	—	—	—	—	—	—	—	—	X

¹ For specimen collection requirements, see [Appendix I](#).

² Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

³ If HIV test results are not available at the visit indicated, provide test results at next available opportunity.

⁴ And microscopy if needed.

⁵ For participants capable of becoming pregnant, pregnancy test may be performed on urine or blood specimens.

Appendix N Protocol Signature Page

A phase 2b study to evaluate the safety and efficacy of VRC01 broadly neutralizing monoclonal antibody in reducing acquisition of HIV-1 infection in women in sub-Saharan Africa

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies

Investigator of Record Name (print)

Investigator of Record Signature

Date

DAIDS Protocol Number: HVTN 703/HPTN 081

DAIDS Protocol Version: Version 4.0

Protocol Date: December 14, 2017

Protocol modification history

Protocol modifications are made to HVTN protocols via clarification memos, letters of amendment, or full protocol amendments. HVTN protocols are modified and distributed according to the standard HVTN procedures as described in the HVTN Manual of Operations (MOP).

The version history of, and modifications to, Protocol HVTN 703/HPTN 081 are described below.

Date: April 2, 2020

Protocol version: Version 4.0

Protocol modification: Clarification Memo 1

- Item 1 Clarified throughout protocol: “Clinic visits”
- Item 2 Clarified in Section 1, *Overview* and Section 6, *Study product preparation and administration*: Study product administration halted

Date: October 3, 2018

Protocol version: Version 4.0

Protocol modification: Letter of Amendment 2

- Item 1 Updated in Section 6.3 and 6.4: Storage conditions for prepared IV bags
- Item 2 Updated in Sections 10 and 15: URLs for accessing DAIDS AE reporting documents

Date: June 15, 2018

Protocol version: Version 4.0

Protocol modification: Letter of Amendment 1

- Item 1 Updated in Section 6.3 and 6.4: Storage conditions for prepared IV bags
- Item 2 Corrected in Section 1, *Overview*: Schema and notes
- Item 3 Updated in Section 1.1, *Protocol Team*: Co-chair institutional affiliation and Consultative investigators
- Item 4 Clarified in Sections 2.4.4 and 5.3.3: Reactive HIV tests and discontinuation of infusions
- Item 5 Revised in Section 1, *Overview* and Appendices F through I: Endpoint lab listings

Date: December 14, 2017

Protocol version: Version 4.0

Protocol modification: Full Protocol Amendment 3

- Item 1 Sample size increased from 1500 to 1900

- Item 2 Added in Appendices A and C: Broad regulatory agency access to participant study records

Date: August 25, 2017

Protocol version: Version 3.0

Protocol modification: Full Protocol Amendment 2

- Item 1 Revised: Study duration and participant follow-up
- Item 2 Updated in Section 1.1: Protocol team membership
- Item 3 Revised in Section 2.4.5, *Trial monitoring*: Feasibility assessment
- Item 4 Updated in Sections 2.9, 2.9.3, 2.9.4, 2.10, and Appendix A: VRC01 clinical experience in HVTN 104
- Item 5 Updated in Section 2.9.5, *Particle formation*, and Section 6.2, *Study product formulation*: Product description and formulation/preparation instructions
- Item 6 Revised in Section 4.7.3: *Monitoring for futility to assess PE*
- Item 7 Clarified in Section 5: Eligibility determination
- Item 8 Clarified in Section 5.2, *Exclusion criteria*: Tissue or organ transplantation exclusion criterion
- Item 9 Clarified in Section 6.4, *Administration*: IV bag label weight and IV tubing flushing
- Item 10 Clarified in Section 7.3, *Enrollment and infusion visits*: Timing of HIV infection assessment and HIV testing
- Item 11 Updated in Section 7.10, *Assessments of reactogenicity*, Section 10.2.2, *AE reporting*, and Section 15, *Document references (other than literature citations)*: DAIDS AE grading table version and exceptions
- Item 12 Updated in Sections 10.2: URLs for referenced documents
- Item 13 Updated in Section 10.2.3: *Expedited reporting of adverse events to DAIDS*
- Item 14 Updated in Section 14: *Version history*
- Item 15 Updated in Section 15, *Document references (other than literature citations)*: Documents and URLs
- Item 16 Updated in Section 16: *Acronyms and abbreviations*
- Item 17 Updated in Appendix A, *Sample informed consent form*: Minimum infusion time
- Item 18 Corrected in Appendix A, *Sample informed consent form*: Blood draw volumes
- Item 19 Clarified in Appendix A, *Sample informed consent form*: Early termination
- Item 20 Revised in Appendix B, *Approved birth control methods (for sample informed consent form)*: Approved contraception methods
- Item 21 Corrected in Appendix D, *Tables of procedures (for sample informed consent form)*: Procedure timepoint

Item 22 Clarified in Appendix F: DBS allowance applies to Visit and 56-day blood draw totals

Item 23 Updated in Appendices F through I: Assay locations and HVTN laboratory listings

Item 24 Revised in Appendices G, H, K, and L: Table format and Schedule 3 blood draws at Visit #.X

Item 25 Clarified in Appendices J and M: Provision of HIV test results

Item 26 Added as Appendix N: Protocol signature page

Item 27 Updated in Sections 6.2 through 6.4 per Clarification Memo 1 to protocol Version 2.0: Study product description, storage, and administration instructions

Item 28 Corrected: Minor typographical, grammatical, and formatting errors

Date: March 8, 2017

Protocol version: Version 2.0

Protocol modification: Clarification Memo 1

Item 1 Updated in Section 6.2, *Study product formulation*: VRC01 description and storage temperature

Item 2 Revised in Sections 6.3 and 6.4: Holding times for study products after preparation

Item 3 Updated in Section 6.4, *Administration*: Minimum infusion time period

Item 4 Added in Section 6.4, *Administration*: In-line filter set requirement

Item 5 Clarified in Sections 6.3.1 and 6.3.2: VRC01 vials with visible particles not to be used

Date: June 24, 2016

Protocol version: Version 2.0

Protocol modification: Full Protocol Amendment 1

Item 1 Study population limited to women in sub-Saharan Africa at risk of acquiring HIV through sexual transmission

Item 2 Added in Section 1, *Overview*: Note regarding enrollment numbers

Item 3 Revised in Section 1, *Overview*, and Section 5.1, *Inclusion criteria*: Participant age range

Item 4 Updated in Section 1.1, *Protocol Team*: Membership and affiliations

Item 5 Clarified in Section 2.1, *Rationale for trial concept*: Worldwide HIV infections and licensure status of VRC01

Item 6 Updated: Section 2.4.5, *Trial monitoring*

Item 7 Updated: Section 2.6, *Plans for future product development and testing*

Item 8 Added in Section 2.8.1, *Protection against challenge in NHP models*: Non-neutralizing mechanisms of bnAb protection in NHP challenge studies

- Item 9 Added in Section 2.9.2, *VRC 602*: Information on serum neutralizing activity and anti-VRC01 antibodies
- Item 10 Updated in Sections 2.9.3 and 2.9.4: Phase 1 clinical trial experience and VRC01 safety summary
- Item 11 Added in Section 2.9.3: VRC01 pharmacokinetics in HVTN 104
- Item 12 Revised in Sections 3.3, 4.8, and 9.6 and Appendix F: PrEP use monitoring
- Item 13 Revised: Section 4, *Statistical considerations*
- Item 14 Clarified in Section 5.1, *Inclusion criteria*: Urine protein measures
- Item 15 Revisions in Section 5.2: *Exclusion criteria*
- Item 16 Clarified in Section 5.3.3, *Discontinuing infusions for a participant*: Participants for whom infusions are stopped for reasons other than HIV infection
- Item 17 Updated in Section 6, *Study product preparation and administration*: Study product regimen, formulation, storage, preparation, and administration instructions
- Item 18 Removed in Section 7.2, *Pre-enrollment procedures*: Required recording of generic names for concomitant medications
- Item 19 Clarified in Section 7.3, *Enrollment and infusion visits*: Urine dipstick and instructions for infusion observation and reactogenicity assessment
- Item 20 Corrected in Section 7.4: *Post-infusion visits for HIV-uninfected study participants*
- Item 21 Corrected in Section 7.5, *HIV counseling and testing*: PrEP information source
- Item 22 Clarified in Section 7.5.1, *Study product-related seroreactivity*: Serum concentrations tested and reference to HIV testing only
- Item 23 Added as (new) Section 7.6: Follow-up visits for HIV-infected participants
- Item 24 Added as (new) Section 7.7 and Appendices I and M: *Follow-up for study participants for whom infusions have been stopped for reasons other than HIV infection*
- Item 25 Corrected in Section 7.8, *Contraception status*: Where to find details regarding contraception requirements
- Item 26 Clarified in Section 7.9 and Appendices F, I, J, and M: Urine testing
- Item 27 Clarified in Sections 7.10, *Assessments of reactogenicity*: Systemic and local signs and symptoms and infusion sites reactions
- Item 28 Revised in Section 7.11, *Visit windows and missed visits*: Visits for performance of safety assessments and local safety labs
- Item 29 Corrected in Section 8.5, *HIV infection during the study*: Visit schedules for HIV-infected study participants
- Item 30 Revised in Section 9.5.1, *Anti-VRC01 antibody assay*: Assay description

- Item 31 Clarified in Section 9.5.2, *Neutralizing antibody* assay: Range of applicability
- Item 32 Clarified in Section 10.1.1, *HVTN 703/HPTN 081 PSRT*: Protocol safety review team membership
- Item 33 Removed in Section 10.1.3, *Roles and responsibilities in safety monitoring*: Reference to planned holds
- Item 34 Added in Section 10.2.2, *AE reporting*: Uterine bleeding secondary to contraception
- Item 35 Added in Section 10.2.2, *AE reporting*: African working hours
- Item 36 Updated in Section 10.2.3, Expedited reporting of adverse events to DAIDS: DAERS support email address
- Item 37 Corrected in Section 10.4.2: PSRT review timing
- Item 38 Clarified in Section 10.4.3: Cumulative safety data reports to DSMB
- Item 39 Removed in Section 10.6, *Social impact reporting*: Reference to Study Specific Procedures (SSP)
- Item 40 Updated in Section 15: URL for DAIDS source documentation requirements
- Item 41 Updated and clarified: Appendix A, Sample informed consent form
- Item 42 Added in Appendix A and (optional) Appendix E: Consent for HIV-infected study participants
- Item 43 Clarified in Appendix A and C consent forms: Potential genetic testing
- Item 44 Added in Appendix A, C, and E consent forms: MCC contact information
- Item 45 Added in Appendix B, *Approved birth control methods*: Injectable contraceptives
- Item 46 Added in Appendix D: Procedure tables for HIV-infected participants and for participants whose infusions have been stopped for reasons other than HIV infection
- Item 47 Clarified in footnotes to Appendix F and J: Pregnancy testing
- Item 48 Clarified in Appendices F, G, and I: HVTN and non-HVTN endpoint laboratories
- Item 49 Added in Appendix F: VRC lab for anti-VRC01 antibody levels
- Item 50 Corrected in Appendices G, H, K, and L: Appendix titles, visit schedules, visit numbering, and procedures
- Item 51 Added in Appendices G and H: Whole blood samples for confirmatory HIV testing
- Item 52 Clarified in Appendix J, *Schedule 1—Procedures at CRS for HIV-uninfected participants*: No participant questionnaire at Visit 0 (screening visit)
- Item 53 Added to Appendices K and L: Local lab assessments

Item 54 Updated and corrected throughout the protocol document: Acronyms, abbreviations, numbering of figures, tables, and appendices, cross-references, and grammatical errors

Date: April 15, 2016

Protocol version: Version 1.0

Protocol modification: Clarification Memo 2

Item 1 Clarified in Appendix I, *Schedule 1—Procedures at CRS for HIV-uninfected participants*: No participant questionnaire during screening

Date: February 22, 2016

Protocol version: Version 1.0

Protocol modification: Clarification Memo 1

Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

[*Note: Clarification Memo 1 dated February 22, 2016 replaces Clarification Memo 1 dated September 4, 2015 and Letter of Amendment 1 dated September 28, 2015.*]

Date: September 28, 2015

Protocol version: Version 1.0

Protocol modification: Letter of Amendment 1

Item 1 Corrected in Appendices G, H, J, and K: Visit schedules

Item 2 Clarified in Appendices J and K: Assessment of HIV/AIDS-related conditions applies to both complete and abbreviated physical exams

Item 3 Removed in Appendices J and K: Social impact assessment questionnaire

Date: September 4, 2015

Protocol version: Version 1.0

Protocol modification: Clarification Memo 1

Item 1 Corrected in Appendices G, H, J, and K: Visit numbering

Item 2 Corrected: Titles of Appendices J and K

Date: August 11, 2015

Protocol version: Version 1.0

Protocol modification: NA

HVTN 704/HPTN 085 and HVTN 703/HPTN 081
Antibody Mediated Prevention Trials Statistical
Analysis Plan for Safety, Trial Monitoring, and
Prevention Efficacy Analysis

October 21, 2016

Study Statisticians

Statistical Center for HIV/AIDS Research and Prevention
Vaccine and Infectious Disease Division
Fred Hutchinson Cancer Research Center

Contents

1	Overview of the Antibody Mediated Prevention Trials	6
2	Objectives and Endpoints of the AMP Trials	6
2.1	Primary Objectives and Endpoints	6
2.2	Secondary Objectives and Endpoints	6
2.3	Exploratory Objectives	7
3	Follow-Up Period	7
4	Study Populations	8
5	Definition of the Primary Efficacy Endpoint (Documented HIV-1 Infection)	9
5.1	HIV Testing Postinfusion	9
5.2	Endpoint Adjudication	9
5.3	Date of the Primary Efficacy Endpoint	10
5.4	Estimated Date of HIV-1 Infection via the ‘Look-Back’ Procedure for HIV-Specific PCR Testing	10
6	Interactions of Study Statisticians with the Data and Safety Monitoring Board	10
7	Statistical Analysis of Safety	11
7.1	Baseline Comparability	11
7.1.1	Reactogenicity	12
7.1.2	AEs and SAEs	12
7.1.3	Local Laboratory Values	12
7.1.4	Reasons for Infusion Discontinuation and Early Study Termination .	12
8	Statistical Analysis of Prevention Efficacy	13
8.1	Primary Analysis of Prevention Efficacy	13

	3
8.2 Secondary Analyses of Prevention Efficacy	14
8.2.1 Prevention Efficacy Accounting for Number of Founding Viruses	18
8.3 Analysis of Exploratory Objective 1	18
8.4 Analysis of Exploratory Objective 2	18
8.5 Analysis of Exploratory Objective 3	19
9 Trial Monitoring	21
9.1 Feasibility Check and Guideline for Continuing Enrollment as Planned . . .	21
9.2 Sequential Monitoring of Prevention Efficacy for Potential Harm, Non-Efficacy, and High Efficacy	25
9.2.1 Potential harm monitoring	26
9.2.2 Non-efficacy monitoring	27
9.2.2.1 Unblinded conditional power assessment at an interim analysis	29
9.2.3 High efficacy monitoring	29
9.2.4 Rationale for starting non-efficacy/high efficacy monitoring at at least 45 total infections	29
9.3 Monitoring of the Use of PrEP	30
9.3.1 Simulation Study for PrEP Monitoring	32
9.4 Monitoring for Futility to Assess PE	33
9.4.1 Calculation of the projected time to the target number of infections at an interim analysis	35
9.4.2 Blinded conditional power assessment at an interim analysis	37
9.5 Operational Analysis Near the End of Enrollment to Decide whether to Con- sider Expanding Enrollment	38
9.6 Monitoring for Performance Standards of Quality of Trial Conduct	38
9.6.1 Expanded details for reporting on item 4: quality and timeliness of HIV-1 diagnostic testing	39
9.6.2 Expanded details for reporting on item 5: quality and timeliness of data collected on case report forms	39
10 Statistical Software	40

	4
11 Roles of Study Statisticians	40
Appendix A	40
References	81

List of Tables

1	Super Learner library for estimation of cumulative incidence of the primary efficacy endpoint in the pooled mAb and the control arms	16
2	Super Learner library for estimation of the conditional probability of the primary efficacy endpoint given measured baseline risk factors	22
3	Summary of sequential monitoring of PE for each AMP trial	26
4	Potential harm monitoring stopping boundaries for each AMP trial	28
5	Estimated rates of PrEP use and estimated percent person-years on effective PrEP use	32

1 Overview of the Antibody Mediated Prevention Trials

The Antibody Mediated Protection (AMP) trials consist of two harmonized protocols, HVTN 704/HPTN 085 and HVTN 703/HPTN 081, which evaluate the safety and efficacy of VRC01, a broadly neutralizing monoclonal antibody (mAb) against the CD4 binding site of the HIV-1 envelope glycoprotein administered in 10 IV infusions every 8 weeks, in reducing acquisition of HIV-1 infection. HVTN 704/HPTN 085 enrolls 2700 HIV-uninfected men and transgender persons (TG) in North and South America (U.S., Switzerland, Peru, Brazil) who have anal sex with men or TG, and HVTN 703/HPTN 081 enrolls 1500 HIV-uninfected sexually active women in sub-Saharan Africa (South Africa, Botswana, Malawi, Kenya, Zimbabwe, Mozambique, and Tanzania). Study participants are randomized to receive a 10 mg/kg or a 30 mg/kg dose of VRC01 or a control preparation. Participants are tested for HIV-1 infection every 4 weeks and at any time following participant report of possible HIV-1 exposure during the study.

2 Objectives and Endpoints of the AMP Trials

HVTN 704/HPTN 085 and HVTN 703/HPTN 081 are two randomized, double-blind, placebo-controlled Phase 2b test-of-concept HIV prevention trials, conducted in HIV-uninfected adults at risk for HIV infection.

2.1 Primary Objectives and Endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

2.2 Secondary Objectives and Endpoints

Planned statistical analyses for secondary objective 1 is described in the separate Correlates of Prevention Efficacy Statistical Analysis Plan.

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available postHIV-infection serum samples

2.3 Exploratory Objectives

Exploratory objective 1:

To assess use of FTC/TDF in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

3 Follow-Up Period

All participants will be followed for 92 weeks (i.e., slightly over 21 months) post-enrollment. Week 80 is the last study visit for the primary efficacy endpoint analysis. Week 92 is the last study visit for the primary analysis of safety and tolerability. Participants who are diagnosed with HIV-1 infection during the study will be followed for approximately 6 months following infection diagnosis.

4 Study Populations

We define three study cohorts that are analyzed for addressing various study objectives. This terminology is used throughout this SAP.

- **Safety Cohort:** all randomized participants who receive the first infusion
- **Modified Intent-to-Treat (MITT) Cohort:** participants in the Safety Cohort who are not later discovered to have been HIV-infected on the date of the first infusion (Day 0)
- **Per-Protocol (PP) Cohort:** MITT participants who receive all planned infusions within the target infusion-visit windows

The Safety Cohort and the MITT Cohort are very similar but not identical to a full Intention-to-Treat Cohort (i.e., all randomized participants); the Safety Cohort differs by excluding randomized volunteers who do not enroll; and the MITT Cohort is a subset of the Safety Cohort that also excludes randomized participants discovered later to have been HIV-positive by Day 0. Due to blinding and the brief length of time between randomization and enrollment (typically no more than 4 working days), we expect almost all randomized participants to be in the Safety Cohort. Given that eligibility for the study requires recent evidence of being HIV-1 uninfected (within 30 days prior to enrollment), we expect almost all enrolled participants to be in the MITT Cohort.

The PP Cohort is defined at each fixed study time point for a participant, with inclusion defined by receiving all planned infusions within the target infusion-visit windows up to that point of time and not yet having an HIV-1 positive diagnostic test result. This time-dependent cohort definition is necessary given that participants experiencing the HIV infection primary endpoint are not given infusions post HIV infection diagnosis. Consequently, the analyses for assessing prevention efficacy in the MITT and PP cohorts handle time differently— the former compare infection rates between treatment groups in the fixed MITT cohort defined at baseline whereas the latter compare infection rates between treatment groups whose membership changes over time based on infusion adherence data. In particular, at a given study time a participant is in the PP cohort if they have not yet been diagnosed with the HIV-1 infection endpoint and they have received all planned infusions within the target infusion-visit windows up to that point of time.

All analyses of safety objectives are based on the Safety Cohort. All analyses of prevention efficacy are based on the MITT cohort unless explicitly demarcated otherwise. Analyses of correlates of prevention efficacy are based on participants in the Marker Cohort (defined in the Correlates of Prevention Efficacy SAP), with additional supportive secondary analyses conducted based on the intersection of the Marker and PP Cohorts.

Prevention efficacy analyses will be based on data from MITT participants treated according to the initial randomization assignment regardless of how many infusions they received (i.e.,

treated “as randomized”). Additionally, secondary efficacy analyses will be performed in the PP Cohort, which will be analyzed on the “as-treated” basis (actually received treatments).

5 Definition of the Primary Efficacy Endpoint (Documented HIV-1 Infection)

5.1 HIV Testing Postinfusion

The prevention efficacy endpoint is diagnosis of HIV-1 infection during the follow-up period. Following enrollment, HIV testing will take place at scheduled clinic visits.

HIV testing is performed using the protocol-specific HIV testing algorithms (see Study-Specific Procedures). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV-1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV-1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit. Samples to be stored for future studies will also be collected at this time.

A ‘case’ is defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s). Only HIV-1 infection cases confirmed by the Endpoint Adjudicator(s) will be counted as HIV-1 infections in the analysis.

5.2 Endpoint Adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess. Therefore, the Endpoint Adjudicator(s) will review all serological and virological test results in a blinded manner for each participant who tests positive per the trials’ diagnostic testing algorithms. The Endpoint Adjudicator(s) will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (i.e., HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the Vaccine Research Center and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

5.3 Date of the Primary Efficacy Endpoint

The Endpoint Adjudicator(s) will define the date of diagnosis based on his/her judgment of all of the available diagnostic data. This date is assigned based only on diagnostic results collected prospectively over time; it does not consider the results of HIV-specific PCR tests that may be performed on earlier samples that are tested later. The date of HIV-1 infection diagnosis will be used as the event-date for primary time-to-event analyses of Primary Endpoint 2 (documented HIV-1 infection).

5.4 Estimated Date of HIV-1 Infection via the ‘Look-Back’ Procedure for HIV-Specific PCR Testing

For all participants diagnosed with HIV-1 infection, the sample available at the nearest date before the diagnosis date will be tested using HIV-specific PCR. If it is positive, then the sample at the second nearest date before the diagnosis date will be tested using HIV-specific PCR. This ‘look-back’ procedure will be repeated until an HIV-specific PCR negative test result is obtained or until a test is done for a Day 0 sample. The default estimate of the date of infection is the midpoint between the last negative and the first positive PCR test result. The estimated infection date may be used as the event-date for marker correlates and sieve analyses of breakthrough HIV-1 infections (see the Correlates of Prevention Efficacy SAP for details) and may also be used for exploratory analyses of the primary efficacy endpoint. The estimator of the date of HIV-1 infection may be refined to be based on additional data beyond the diagnostic testing information (details of this estimator are described in the Correlates of Prevention Efficacy SAP).

6 Interactions of Study Statisticians with the Data and Safety Monitoring Board

At each 6-monthly Data and Safety Monitoring Board (DSMB) meeting, the study statisticians will present Open and Closed Reports separately for each AMP trial; all tables and

figures included in the Closed Report are specified in Appendix A with statistical analyses of safety further described in Section 7. For a subset of tables and figures in the Closed report, the Open Report includes tables and figures with the same information except with trial information presented pooled across the three treatment groups to preserve blinding to treatment assignment. In addition, the following trial monitoring reports will be presented at each DSMB meeting, separately for each AMP trial:

- feasibility monitoring report per Section 9.1 starting after approximately and not fewer than 120 enrolled participants have expected follow-up through to the end of the Week 32 visit;
- monitoring report of prevention efficacy for potential harm, non-efficacy, and high efficacy per Section 9.2, where
 - potential harm monitoring is commenced at the 20th pooled primary efficacy endpoint and is continually performed with each additional endpoint until the time non-efficacy/high efficacy monitoring is triggered,
 - non-efficacy monitoring is commenced at at least 45 but no more than 67 pooled primary efficacy endpoints, and
 - high efficacy monitoring is commenced at the same time as non-efficacy monitoring;
- monitoring report for the use of Truvada as pre-exposure prophylaxis per Section 9.3;
- monitoring report for futility to assess prevention efficacy per Section 9.4 starting after at least 12 months after the first participant is enrolled;
- operational analysis report for enrollment expansion considerations per Section 9.5 at approximately 3 months before planned enrollment completion; and
- monitoring report for performance standards of quality of trial conduct per Section 9.6.

7 Statistical Analysis of Safety

Since enrollment is concurrent with receiving the first infusion, all enrolled participants will have received at least 1 infusion and therefore will provide some safety data.

7.1 Baseline Comparability

Treatment groups will be compared for baseline characteristics including demographics and laboratory measurements, using descriptive statistics (percentages, means, ranges).

7.1.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participants reactogenicity will be counted once under the maximum severity for all infusion visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

7.1.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

7.1.3 Local Laboratory Values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

7.1.4 Reasons for Infusion Discontinuation and Early Study Termination

The number and percentage of participants who permanently discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

8 Statistical Analysis of Prevention Efficacy

Except where specified, all prevention efficacy endpoint analyses are performed in the MITT cohort. All analyses only use samples and data collected prior to study unblinding. The final prevention efficacy analysis will occur when the last enrolled participant has reached the Week 80 visit.

8.1 Primary Analysis of Prevention Efficacy

The time between randomization and the date of HIV-1 infection diagnosis determined according to Section 5.3 is evaluated in the MITT cohort. The failure times of participants never observed to be diagnosed with HIV-1 infection are right-censored at the date of the last HIV-negative test or the Week 80 visit, whichever occurs earlier.

Let PE denote the overall prevention efficacy by Week 80 of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. We define the primary PE parameter as

$$PE = \{1 - \text{cumulative incidence ratio (pooled mAb groups/control group)} \\ \text{of the primary efficacy endpoint by 80 weeks}\} \times 100\%, \quad (1)$$

where the cumulative incidence ratio is the probability of the primary efficacy endpoint by the Week 80 visit for participants assigned to receive the mAb divided by the probability of the primary efficacy endpoint by the Week 80 visit for participants assigned to receive control.

Each of the two cumulative incidence parameters in (1) will be estimated using the transformed Nelson-Aalen estimator for the cumulative hazard function evaluated at Week 80. We will use the delta method to obtain the asymptotic 95% CI for the log cumulative incidence ratio (pooled mAb/control) and then back-transform these confidence bounds to the PE scale. Both the point estimate and the 95% CI for PE will be reported. In addition, if there are more than 10 HIV infection events in each of the VRC01 dose groups, then the above estimators will be computed separately for each dose group and aggregated for inference on PE.

PE is the target parameter for the primary analysis of overall PE. The primary analysis tests the null hypothesis

$$H_0 : PE = 0\% \text{ versus the alternative hypothesis } H_1 : PE \neq 0\% \quad (2)$$

using a 2-sided $\alpha = 0.05$ level Wald test of the equality of log cumulative hazard functions at 80 weeks for the pooled mAb group and the control group. Note that the critical value for determining whether the effect of VRC01 on prevention of HIV-1 acquisition is significant at the two-sided 0.05 level will not require adjustment for the interim monitoring of PE

for potential harm, non-efficacy, and high efficacy described in Section 9.2. This is because this monitoring is designed to have minimal impact on the type-I error/power of the study. Moreover, whereas interim monitoring for positive PE would mean that the actual type-I error of the study is inflated above the nominal level, interim monitoring for potential harm, non-efficacy, and high efficacy has the effect of decreasing the actual type-I error rate below the nominal level. In other words, use of the unadjusted critical value leads to conservative (as opposed to anti-conservative) inference, and our simulations show that the degree of conservatism is minimal.

The timing of infections will be described separately for the pooled mAb group and the control group by the respective cumulative incidence curves of the time between first infusion and the date of HIV-1 infection diagnosis. Each curve will be estimated by a transformed Nelson-Aalen estimator for the cumulative hazard function. To obtain a pointwise 95% CI, we will use the delta method to obtain the asymptotic 95% CI for the log cumulative incidence over time and then exponentiate the confidence bounds. As for PE, if there are more than 10 HIV infection events in each of the VRC01 dose groups, then the above estimators will be computed separately for each dose group and aggregated for inference on the pooled mAb group cumulative incidence.

Additionally, cumulative PE over time will be reported. To obtain pointwise 95% CIs, first we will use the delta method to obtain asymptotic 95% CIs for the log cumulative incidence ratio (pooled VRC01/control) over time and then back-transform the confidence bounds to the PE scale. The simultaneous 95% confidence interval for cumulative PE over time will be obtained following the method of Parzen, Wei, and Ying (1997).

8.2 Secondary Analyses of Prevention Efficacy

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall prevention efficacy of the 10 mg/kg mAb group and let PE30 be the overall prevention efficacy of the 30 mg/kg mAb group, defined as

$$PE10 = \left\{ 1 - \text{cumulative incidence ratio (mAb 10 mg/kg group/control group)} \right. \\ \left. \text{of the primary efficacy endpoint by 80 weeks} \right\} \times 100\%,$$

and

$$PE30 = \left\{ 1 - \text{cumulative incidence ratio (mAb 30 mg/kg group/control group)} \right. \\ \left. \text{of the primary efficacy endpoint by 80 weeks} \right\} \times 100\%.$$

The PE10 and PE30 parameters will be assessed using the same estimation method as described in Section 8.1.

We will conduct secondary analyses to test the null hypotheses

$$H_0 : PE10 = 0\% \text{ versus the alternative hypothesis } H_1 : PE10 \neq 0\%$$

and

$H_0 : PE30 = 0\%$ versus the alternative hypothesis $H_1 : PE30 \neq 0\%$

using 2-sided $\alpha = 0.05$ level Wald tests described in Section 8.1. Both unadjusted p-values and Holm–Bonferroni-adjusted p-values (Holm, 1979) will be reported for each of the individual dose versus control group analyses.

In addition, the following secondary analyses of PE will be conducted:

- (i) Assess a dose-response effect by testing the null hypothesis

H_0 : cumulative HIV-1 incidence by 80 weeks is equal in the three study groups versus $H_1 : 0\% \leq PE10 \leq PE30$ with at least one strict inequality.

- (ii) Test the null hypothesis that the cumulative HIV-1 incidence by 80 weeks is equal in the three study groups versus the alternative hypothesis that there are some differences.
- (iii) Test the null hypothesis that the cumulative HIV-1 incidence by 80 weeks is equal in the two mAb groups versus the alternative hypothesis that PE30 is greater than PE10, which would demonstrate that assignment to a higher mAb dose level causes higher PE.

Hypotheses (i)–(iii) will be tested using cumulative hazard function based Wald tests. Define the Wald test statistic

$$W_{i,j} = \frac{\log \hat{\Lambda}_i(80 \text{ weeks}) - \log \hat{\Lambda}_j(80 \text{ weeks})}{\sqrt{\widehat{\text{var}}\{\log \hat{\Lambda}_i(80 \text{ weeks})\} + \widehat{\text{var}}\{\log \hat{\Lambda}_j(80 \text{ weeks})\}}},$$

where $\hat{\Lambda}(\cdot)$ is the Nelson-Aalen estimator and $i, j \in \{c, 10, 30\}$, $i \neq j$, represent the control, 10 mg/kg mAb, and 30 mg/kg mAb group, respectively. The test statistic considers the estimated variance of the Nelson-Aalen estimator proposed in Aalen (1978).

The alternative hypothesis in (i) is equivalent to $\tilde{H}_1 : \Lambda_c(t_0) \geq \Lambda_{10}(t_0) \geq \Lambda_{30}(t_0)$, $t_0 = 80$ weeks, with at least one strict inequality, and therefore the test of (i) will reject H_0 if both $W_{c,10} \geq \Phi^{-1}(0.975)$ and $W_{10,30} \geq \Phi^{-1}(0.975)$, where Φ^{-1} is the quantile function of the standard normal distribution. The test of (ii) will reject H_0 if at least one of $|W_{c,10}| \geq \Phi^{-1}(0.975)$ and $|W_{10,30}| \geq \Phi^{-1}(0.975)$ holds. The test of (iii) will reject H_0 if $W_{10,30} \geq \Phi^{-1}(0.975)$.

As a supportive analysis of the hypotheses in (2), targeted minimum loss-based estimation (TMLE) may be used to estimate cumulative incidences of the primary efficacy endpoint over time for the pooled mAb arm and the control arm. Iterative mean-based TMLE is used for this analysis as described in Benkeser, Carone, and Gilbert (2016). The Super Learner (van der Laan, Polley, and Hubbard, 2007) is used to generate initial estimates of the conditional censoring distribution and the iterated conditional means. The Super Learner

Table 1: Models included in the Super Learner library. Z denotes a mAb group assignment, B baseline behavioral risk score as described in Section 8.5, and W a vector of baseline demographic covariates. The columns indicate what type of model was used (glm = generalized linear model, step = stepwise glm using both AIC and BIC as selection criteria, and gam = generalized additive model), how time was modeled ($\emptyset$ denotes time was omitted from the model, **factor(t)** indicates dummy variables were used), and what covariates were included ($x * y$ indicates a cross product between covariates x and y). We use $s(x; df = d)$ to denote that variable x was modeled using a polynomial spline of degree d .

Model type	Time	Covariates
Conditional mean estimates		
glm	$\emptyset$	Z
glm	$\emptyset$	$Z + B + W$
glm	$\emptyset$	$Z * B$
step	$\emptyset$	$Z * B + W$
Censoring estimates		
glm	factor(t)	$\emptyset$
glm	factor(t)	$Z * t$
glm	$\emptyset$	Z
glm	$\emptyset$	$Z + B + W$
glm	t	Z
glm	t	$Z + B + W$
glm	$\log(t)$	Z
glm	$\log(t)$	$Z + B + W$
step	factor(t)	$Z + B + W$
step	t	$Z + B + W$
step	$\log(t)$	$Z + B + W$
gam	$s(t, 3)$	Z
gam	$s(t, 3)$	$Z + B + W$
gam	$s(t, 2)$	Z
gam	$s(t, 2)$	$Z + B + W$

library includes both parametric and nonparametric algorithms: generalized linear models, generalized additive models with 2 or 3 degrees of freedom, a regression tree (Breiman et al., 1984), and a random forest (Breiman, 2001) (specified in Table 1). Each method considers adjustment for baseline demographic covariates, the baseline behavioral risk score built via supervised learning as described in Section 8.5, and two-way interactions of these terms. The candidate algorithms in the Super Learner library consider various adjustments for time, as shown in Table 1.

PE parameters will be estimated by 1 minus the ratio (pooled mAb groups/control group)

of these tMLE estimators. Influence-curve based variance estimators of each cumulative incidence is used, and the delta method applied to obtain the variance estimator of the log cumulative incidence ratio. Point estimates and 95% pointwise and simultaneous Wald CIs for cumulative incidence curves and $PE(t)$ curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of the primary efficacy endpoint over time, secondary analyses will assess hazard ratio based PE defined as

$$PE = \{1 - \text{hazard ratio (pooled mAb groups/control group)} \\ \text{of the primary efficacy endpoint at 80 weeks}\} \times 100\%. \quad (3)$$

The PE parameter in (3) will be estimated using a Cox proportional hazards model with the indicator of assignment to a mAb group versus the control group as the sole covariate. The score test will be used to evaluate whether hazard ratio PE differs from zero. This analysis uses the same failure time as used for the primary analysis of the cumulative-incidence based PE. Goodness-of-fit diagnostics including the complementary log-log endpoint-free survival curves and the Grambsch and Therneau (1994) test will be applied to assess veracity of the proportional hazards assumption. If there are more than 10 HIV infection endpoint for each of the mAb dose groups, then separate baseline hazards for the two dose groups will be used.

An additional secondary analysis of PE based on the Cox proportional hazards model will be done that uses as the failure time variable the time from the most recent infusion to the estimated date of HIV-1 infection as a time-dependent covariate. This analysis can have increased power to detect prevention efficacy compared to the primary analysis of the cumulative incidence based parameter PE, if instantaneous prevention efficacy is higher when VRC01 concentrations are higher. Goodness-of-fit diagnostics will be applied as described above.

The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity and interpretation of the primary analysis does not depend on the proportional hazards assumption.

The Cox model will also be used for a secondary analysis to assess PE in the PP cohort by modeling full cumulative infusion adherence (i.e., at study time t , all infusions up to and including time t received within target visit windows) or lack thereof as a binary time-varying covariate. In addition, to study the dose-response in the association of infusion adherence with PE, we will assess PE in subgroups defined by the level of cumulative infusion adherence over time, with adherence levels defined, at time t , as missing zero infusions by time t , missing at most 1 infusion by time t , missing at most 2 infusions by time t , etc., included in the model as binary time-varying covariates. If there is a time-varying covariate prognostic for subsequent HIV-1 infection that also predicts the probability of subsequently taking infusions, and taking infusions predicts subsequent values of this prognostic factor, then the Cox model described above provides biased inference (Hernán et al., 2000). Based on this, diagnostics will be done to check if there are any measured time-varying covariates

strongly associated with both infection and taking subsequent infusions. If such covariates are identified, then the standard Cox model analysis described above will be supplemented with a causal structural nested Cox model analysis, which is designed to correct for time-varying confounding.

Sensitivity analyses of the primary analysis will test $H_0 : PE = 0\%$ with a log-rank test and with a Gehan-Wilcoxon test stratified by VRC01 dose group.

To further explore potential time-variations in PE from Week 0 through to Week 80, instantaneous PE over time, defined as one minus the instantaneous hazard ratio (pooled VRC01/control) over time, will be estimated using the nonparametric kernel estimation method with optimal bandwidth selection for the instantaneous hazard ratio as described in Andersen et al. (1993), with an asymptotic pointwise 95% CI. The simultaneous 95% confidence interval for instantaneous PE will be calculated following the method of Gilbert et al. (2002).

8.2.1 Prevention Efficacy Accounting for Number of Founding Viruses

Another secondary analysis may be conducted to assess the effect of VRC01 on prevention of HIV-1 acquisition over 80 weeks using the method of Follmann and Huang (2015) that incorporates information on the number of HIV-1 founder viruses in HIV-1-infected participants. The method has increased efficiency relative to Cox proportional hazards regression if the vaccine reduces the number of founders.

8.3 Analysis of Exploratory Objective 1

The use of oral FTC/TDF as PrEP will be assessed as described in Section 9.3.

8.4 Analysis of Exploratory Objective 2

If there is substantial PrEP use detection at baseline, then the Cox model will be used to assess whether prevention efficacy significantly differs in subgroups with detectable versus undetectable baseline PrEP use, and to make inferences on prevention efficacy separately in each subgroup. In addition, if there is substantial PrEP use detected over the course of the study, then a Cox model with PrEP detectability as a time-varying covariate will be used to assess different prevention efficacy by time-varying subgroup and for each subgroup separately.

More specifically, the primary analysis will be repeated where only MITT infection endpoints with no evidence of PrEP use at the time of HIV-1 diagnosis and at the time of the earliest evidence of infection will be included in the analysis. Intracellular TFV concentration (see Section 8.3) will be used to determine eligibility for this analysis. A participant is eligible

if the TFV concentration is below the lower limit of detection as defined above at the diagnosis visit and at the visit with earliest evidence of HIV-1 infection (if different from the diagnosis visit). Since the ARVs are only detectable in plasma for roughly 14 days (Patterson et al. 2010) and some participants may have become infected before the 14-day window, with this approach we are not assured that all those included in the analysis were not using prophylactic ARVs at the time of infection. Therefore an additional analysis may be conducted that addresses this issue by also excluding participants from the HIV-1 acquisition analysis if they self-reported ARV use in the last 30 days at either the diagnosis visit or the last visit prior to diagnosis. These analyses will evaluate uninfected participants without accounting for data on their TFV concentrations.

8.5 Analysis of Exploratory Objective 3

Several analyses will make use of a baseline behavioral risk score variable. This section describes how this variable will be constructed.

Let Y denote the primary efficacy endpoint indicator (i.e., $Y = 1$ if the endpoint was observed and $Y = 0$ otherwise) and W a vector of behavioral risk factors collected in a baseline questionnaire. For the i^{th} participant, we define the baseline behavioral risk score as $\hat{P}(Y_i = 1 \mid W_i)$, where we use loss-based super-learning to estimate the best model for $P(Y = 1 \mid W) = E_0[Y \mid W]$ where E_0 denotes expectation under the true data generating distribution. This is a standard prediction problem. We estimate $E_0(Y \mid W)$ with a minimizer of the risk of a loss: $\psi_0 = \arg \min_{\psi} P_0 L(\psi)$, with $Pf \equiv \int f(o) dP(o)$. We select binary log-likelihood loss $L(\psi)(O) = -\{Y \log \psi(W) + (1 - Y) \log(1 - \psi(W))\}$, given its good performance for a rare event outcome. In order to construct an optimal estimator among any given class of candidate estimators, we use loss-based super-learning. In that manner, the oracle inequality for the cross-validation selector guarantees that the estimator is asymptotically at least as good as any candidate in the set of candidate estimators. We refer to van der Laan, Polley, and Hubbard (2007) and Rose and van der Laan (2011).

Let $\hat{\Psi}_j : \mathcal{M}_{NP} \rightarrow \Psi(\mathcal{M})$ be a candidate estimator that maps an empirical distribution of $(O_1, \dots, O_n)$ (i.e., an element of the nonparametric model $\mathcal{M}_{NP}$ of probability distributions) into the parameter space $\Psi(\mathcal{M}) = \{\Psi(P) : P \in \mathcal{M}\}$, $j = 1, \dots, J$. This library of candidate estimators could include a variety of parametric model based estimators as well as a variety of machine learning algorithms, possibly coupled with different dimension reduction strategies, and possibly indexed by a variety of tuning parameters.

Let $B_n \in \{0, 1\}^n$ be a random split of the sample into a training sample $\{i : B_n(i) = 0\}$ and validation sample $\{i : B_n(i) = 1\}$. For example, if we use V -fold cross-validation defined by a partitioning of the sample in V equal size groups, then B_n has V possible realizations, each occurring with probability $1/V$, and each split corresponds with setting the components of B_n in one of the V -folds equal to 1 and setting the other components equal to 0. Let P_{n, B_n}^0 and P_{n, B_n}^1 be the empirical distributions of the training and validation sample corresponding

with split-vector B_n , respectively. The cross-validated risk of the j -th candidate estimator is then defined as $E_{B_n} P_{n,B_n}^1 L(\hat{\Psi}_j(P_{n,B_n}^0))$.

One could now define the cross-validation selector

$$J_n = \arg \min_j E_{B_n} P_{n,B_n}^1 L(\hat{\Psi}_j(P_{n,B_n}^0))$$

as the selector of the winner, and the corresponding discrete super-learner is then defined as $\hat{\Psi}(P_n) = \hat{\Psi}_{J_n}(P_n)$. One could also propose a parametric family $\{f_\alpha : \alpha\}$ of functions from $\mathbb{R}^J$ to the real line that represents a family of combinations of all the J estimators:

$$\hat{\Psi}_\alpha(P_n) = f_\alpha(\hat{\Psi}_j(P_n) : j = 1, \dots, J),$$

and where α represents a multivariate vector. For example, one might define $\hat{\Psi}_\alpha = \sum_{j=1}^J \alpha_j \hat{\Psi}_j$ as a weighted linear combination of the candidate estimators, where the weights α_j are restricted to be non-negative and sum to 1. One now defines the cross-validation selector for this continuous family of candidate estimators $\{\hat{\Psi}_\alpha : \alpha\}$ accordingly:

$$\alpha_n = \arg \min_\alpha E_{B_n} P_{n,B_n}^1 L(\hat{\Psi}_\alpha(P_{n,B_n}^0)).$$

The super-learner is then defined as $\hat{\Psi}(P_n) = \hat{\Psi}_{\alpha_n}(P_n)$.

By the oracle inequality for the cross-validation selector we have that, if the expectation of the loss-based dissimilarity $\min_\alpha E_{B_n} P_0 \{L(\hat{\Psi}_\alpha(P_{n,B_n}^0)) - L(\psi_0)\}$ between the oracle selected estimator and ψ_0 converges to zero at a slower rate than $1/n$, then

$$\frac{E_0 E_{B_n} P_0 \{L(\hat{\Psi}_{\alpha_n}(P_{n,B_n}^0)) - L(\psi_0)\}}{E_0 \min_\alpha E_{B_n} P_0 \{L(\hat{\Psi}_\alpha(P_{n,B_n}^0)) - L(\psi_0)\}} \rightarrow 1, \text{ as } n \rightarrow \infty.$$

In other words, excluding the unrealistic situation in which one of our candidate estimators is a correctly specified parametric model, the super-learner is asymptotically equivalent with the oracle selected estimator.

In addition, we can evaluate the super-learner by its cross-validated risk, using a cross-validation scheme S_n (e.g., using V -fold cross-validation again as in the super-learner):

$$\text{CV-RISK} = E_{S_n} P_{n,S_n}^1 L(\hat{\Psi}(P_{n,S_n}^0)),$$

which involves rerunning the super-learner on learning samples $\{i : S_n(i) = 0\}$ and evaluating it on test samples $\{i : S_n(i) = 1\}$, and averaging the performance across the different splits.

This represents an estimator of the true conditional risk

$$E_{S_n} R(\hat{\Psi}(P_{n,S_n}^0) \mid P_0) \equiv E_{S_n} P_0 L(\hat{\Psi}(P_{n,S_n}^0)),$$

and one can also construct a Wald-type 95% confidence interval for the latter true conditional risk parameter $E_{S_n} R(\hat{\Psi}(P_{n,S_n}^0) \mid P_0)$ given by $\text{CV-RISK} \pm 1.96\sigma_n/\sqrt{n}$, where $\sigma_n^2 =$

$E_{S_n} P_{n,S_n}^1 \left\{ L(\hat{\Psi}(P_{n,S_n}^0)) - E_{S_n} P_{n,S_n}^1 L(\hat{\Psi}(P_{n,S_n}^0)) \right\}^2$. The theory behind the asymptotic correctness of this data adaptive confidence interval is given in Hubbard, Kherad-Pajouh, and van der Laan (2016). We build the super-learner using the R package *superlearner* available at CRAN.

We will use super-learner with 1-fold cross-validation, separately for the vaccine and placebo groups; 1-fold is selected because it often performs well for small sample size data sets (with only 20–50 endpoint cases expected). Appendix A Table 3 shows the input behavioral risk variables and Table 2 shows the input learners. We will plot point and 95% CI estimates of the cross-validated area-under-the-ROC curves (AUCs) (Hubbard, Kherad-Pajouh, and van der Laan, 2016) for each individual learning approach as well as for discrete super-learner and super-learner, and select the learner with the lowest cross-validated AUC for finalizing the risk scores $\hat{P}(Y_i = 1 | W_i)$. We will report the cross-validated AUC of the best model as a summary of the quality of the risk score.

9 Trial Monitoring

The AMP trials are monitored in four ways: (1) feasibility monitoring for retention and adherence to infusions; (2) sequential monitoring of prevention efficacy; (3) monitoring for futility to assess prevention efficacy, defined as an inability to answer the primary efficacy objective in a timely manner; and (4) operational monitoring for other performance standards of quality of trial conduct. Data on these monitoring activities are collated into interim reports and are presented to the independent DSMB every 6 months. While guidelines for trial modifications based on the monitoring operate separately for the two AMP trials, the same multinational DSMB monitors the two trials, facilitating its ability to account for all information when making recommendations. Following each DSMB meeting, the DSMB reports to the Oversight Committee (OC) a summary of the trial review, which may include recommendations to modify or terminate the trial for one or both study cohorts. The following descriptions apply to each trial separately.

9.1 Feasibility Check and Guideline for Continuing Enrollment as Planned

A feasibility monitoring report is developed as soon as approximately and not fewer than 120 enrolled participants have expected follow-up through to the end of the Week 32 visit window. This feasibility monitoring is based on the first four 8-week infusion intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of participants attend clinical visits and receive the infusions per the protocol.

The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) supplemented by data on visit

Table 2: Learners (xx algorithms/learners) used in the super-learner for building the baseline behavioral risk score for the AMP trials.

Learners	
Stepwise LR^a	Best logistic regression model by AIC through a step-wise search
All Subsets	Best logistic regression model by AIC of all ≤ 5 variable combinations
Gam Step^b	Best generalized additive model (gam ^d) with 2 or 3 degrees of freedom, selected by AIC via step-wise search
Lasso	
Regression tree^c	
Random forest^d	
Discrete SL	van der Laan, Polley, and Hubbard (2007)
Super-learner	van der Laan, Polley, and Hubbard (2007)

^a The step-wise search begins with the full (all input variables) model. On the first step, it fits all remove-one-variable models and then removes one variable based on lowest AIC of the remove-one models. For next and subsequent steps, all models dropping or adding one variable are checked and a variable is dropped or added based on the model with lowest AIC. This procedure is repeated until no add-one-variable or drop-one-variable model has lower AIC than the current model.

^b The generalized additive model step-wise search proceeds in similar manner as the step-wise logistic model search, beginning with the full model with no smoothing. Only the quantitative variables are considered for smoothing. On the first step, it fits all remove-one-variable models, all models with a single quantitative variable smoothed at 2 degrees of freedom and all models with a single quantitative variable smoothed at 3 degrees of freedom, and then selects the model based on lowest AIC. For next and subsequent steps, all models dropping or adding 1 variable and all models changing variables to 2 or 3 degrees of smoothing one at a time are checked and a variable is dropped, added, or changed based on the model with lowest AIC. This procedure is repeated until no add-one-variable, drop-one-variable, or change-one-variable model has lower AIC than the current model.

^c Breiman et al. (1984)

^d Breiman (2001)

attendance, which corresponds to adherence to receipt of infusions.

As stated in the protocol, the following guideline is used for continuing enrollment as planned:

- Continued participation by the Week 32 visit pooled over the three treatment groups is greater than 80%.

If this treatment group-blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is

warranted.

Here we expand upon the details of the feasibility guideline and on the output included in the feasibility check monitoring report.

Discontinued participation is assessed using multiple event definitions indicating discontinued participation, in order to capture different reasons for discontinuation that have different impacts on the ability of the trials to meet their primary efficacy objectives. In particular, the following seven definitions (with their purposes summarized) will be analyzed:

1. CRF-confirmed study termination or permanent discontinuation of study product administration prior to study completion, with discontinuation due to a safety issue or refusal to continue taking infusions. [*Addresses if infusions are too onerous*]
2. The same as Definition 1 except only including discontinuation due to a safety issue [*Addresses if infusions are too onerous due to a safety issue*]
3. The same as Definition 1 except only including discontinuation due to refusal to continue undergoing infusions. [*Addresses if infusions are considered too onerous due to a non-safety reason*]
4. CRF-confirmed study termination, with termination reason lost contact with participant. [*Addresses loss to follow-up, with no information available on whether the loss was related to infusions being onerous*]
5. Occurrence of the Definition 4 event or the event of 20 consecutive weeks without any participant contact, whichever occurs first. [*Addresses loss to follow-up as in Definition 4, except adding an operational definition of loss to follow-up that captures more loss events*]
6. The first event of Definitions 1 and 4 [*Addresses discontinued infusions for any reason—safety, refusal, or loss to follow-up*]
7. The first event of Definitions 1 and 5 [*Addresses discontinued infusions for any reason—safety, refusal, or loss to follow-up including an operational definition of loss to follow-up*]

Definition 1 aims to measure discontinued participation due to the infusion process being too onerous, which could occur either because of a safety issue or because of refusal to continue receive infusions. Definitions 2 and 3 measure discontinued participation due to the two component events comprising Definition 1 (safety and refusal, respectively), thereby isolating two reasons for discontinued infusions. These types of discontinued participation are the most serious in that a high rate would indicate an infeasibility of the VRC01 intervention, and therefore Definitions 1, 2, 3 are the most important for measuring feasibility of the intervention. As such the 80% feasibility guideline is interpreted primarily for Definition 1.

Definitions 4 and 5 measure discontinued participation due to loss to follow-up, with the former definition based on CRF-confirmed loss to follow-up and the latter definition based on either CRF-confirmed loss or an operational definition of a loss to follow-up event not captured on a CRF. These definitions isolate the loss to follow-up component reason of discontinued participation. Given that loss to follow-up is expected to frequently occur for reasons different from the infusion process being too onerous (i.e., for reasons that would occur in efficacy trials of other HIV prevention interventions, such as moving), this type of discontinued participation is less serious, where the study could still be made feasible under moderate rates of loss to follow-up, by enrolling additional study participants.

Two definitions of loss to follow-up are used, because measuring loss only based on CRF-confirmed discontinued participation as in Definition 4 may miss some loss events that occur before a clinical site registers study termination on the CRF. To capture more losses to follow-up, Definition 5 also counts as loss the event of 20 consecutive weeks without any participant contact (20 weeks represents two consecutive planned infusions, with 4 weeks of margin for variability in infusion visit windows). Moreover, a sensitivity analysis may be done that repeats the analysis for a spectrum of working definitions of operational loss to follow-up that use different numbers of consecutive weeks without contact.

Definitions 6 and 7 count as discontinued participation any of the three reasons based on safety, refusal, or lost to follow-up, whichever occurs first. Thus these definitions measure permanent ceasing of infusions without distinguishing the reason.

For each definition of discontinued participation, the analysis counts discontinued participation events. First, we define discontinued participation as a record on a CRF confirming study termination or permanent discontinuation of study product administration prior to study completion, with discontinued participation by Week 32 defined as this date occurring before or on the Week 32 visit date, or, if the visit was not yet attended, before or on the date defining the end of the Week 32 visit window. For Definitions 6 and 7, the Kaplan-Meier estimator will be used to estimate and display the probability of discontinued participation over time, starting at study entry through to the time period during which data are available (which will extend at least through the Week 32 visit window). For all of the other definitions, a competing risks failure time analysis is used that studies the time until the first event of a type specified in a given definition. For these competing risks analyses a participant's follow-up is right-censored by the occurrence of another discontinuation event type that is not included in the definition under consideration. For these competing risks analyses each time-to-event curve is estimated using the Aalen-Johansen estimator, which in particular yields an estimate of the probability of discontinuation due to the event type by the Week 32 visit. For Definition 1 right-censoring is by loss to follow-up (using the operational Definition 5); for Definition 2 right-censoring is by loss to follow-up (using the operational Definition 5) and by discontinuation due to refusal; for Definition 3 right-censoring is by loss to follow-up (using the operational Definition 5) and by discontinuation due to a safety issue; and for Definitions 4 and 5 right-censoring is by discontinuation due to Definition 1 (a safety issue or refusal).

Appendix A includes mock tables on expected versus observed visit attendance (Table 5A) and on infusion adherence (Table 5B) patterns that will be reported at the 6-monthly DSMB meetings. All of this output will be included in the feasibility check monitoring report, focusing on the first five infusion visits (Week 0, 8, 16, 24, 32).

9.2 Sequential Monitoring of Prevention Efficacy for Potential Harm, Non-Efficacy, and High Efficacy

For each trial, PE is monitored by the independent DSMB at each DSMB meeting, with triggers based on numbers of primary HIV-1 infection endpoints for when the DSMB meetings begin to include formal evaluation of the potential harm, non-efficacy, and high efficacy stopping boundaries (these triggers are described below). The approach to sequential monitoring of PE is similar to that described in Gilbert, Grove et al. (2011). The monitoring of PE in the AMP trials is also similar to that used for the HVTN 505 phase 2b HIV-1 vaccine efficacy trial (Hammer et al., 2013). Each of the AMP trials uses sequential monitoring of the pooled mAb groups versus control to stop early for:

- potential harm [establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring-adjusted 90% confidence interval lying below 0%]
- non-efficacy [establish that PE (pooled over the mAb groups) $< 40\%$ based on a 2-sided 95% nominal confidence interval lying below 40%]
- high efficacy [establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal confidence interval lying above 70%].

The sequential monitoring for non-efficacy and high-efficacy is based on 2-sided 95% confidence intervals in order that the result of the study that would be reported in the abstract of a journal article would convey convincing evidence supporting the conclusion of non-efficacy or high efficacy. Freidlin, Korn, and Gray (2010) discuss a rationale for this approach to non-efficacy monitoring. The sequential monitoring for potential harm is based on 2-sided 90% confidence intervals for prudence to protect the safety of study participants, i.e., less precision is required to meet a guideline for potential harm than to meet guidelines about non-efficacy or high efficacy. The sequential monitoring plan for each AMP trial is summarized in Table 3.

The potential harm monitoring is done after every primary endpoint event starting at the 20th total pooled over the three treatment groups, through to the time at which the non-efficacy/high efficacy monitoring commences. Once the non-efficacy/high efficacy monitoring begins, the non-efficacy monitoring serves the purpose of detecting a harmful effect of the mAb to elevate the endpoint rate compared to control. The details of the procedures used for the three monitoring types are described next.

Table 3: Summary of sequential monitoring of PE for each AMP trial

Monitoring Type	Hypotheses	Testing Approach	Size/Power	Monitoring Plan	Number of Interim Analyses
Potential Harm	$H_0 : PE \geq 0\%$ vs. $H_1 : PE < 0\%$	Exact 1-sided binomial test of the proportion of infections assigned to a mAb group	1-sided $\alpha = 0.05$	Near-constant* 1-sided p-value cut-off controlling the FWER at $\alpha = 0.05$	After every infection from 20 th total until first non-efficacy analysis
Non-Efficacy	$H_0 : PE \geq 40\%$ vs. $H_1 : PE < 40\%$	Wald test	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI supplemented with conditional power	6-monthly starting after at least 45 but no more than 67 total infections [†]
High Efficacy	$H_0 : PE \leq 70\%$ vs. $H_1 : PE > 70\%$	Wald test	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI	6-monthly starting at the same time as for non-efficacy

*An increasing per-test alpha until a constant level is reached that, if applied to all subsequent tests, maintains the specified FWER

[†]The first non-efficacy/high efficacy interim analysis occurs either at the scheduled DSMB meeting at which there are 45 or more primary endpoint events across the three study groups or when 67 total primary endpoint events are observed, whichever occurs earlier.

9.2.1 Potential harm monitoring

Heyse et al. (2008) and the HVTN 505 phase 2b HIV-1 vaccine efficacy trial (Hammer et al., 2013) are examples of randomized, placebo-controlled efficacy trials that used continuous monitoring for an elevation in the endpoint rate in the active versus control treatment arm. Continuous monitoring means that an unblinded statistician has visibility to the treatment assignment of each diagnosed MITT HIV-1 infection as they are determined in real-time, and, after each confirmed HIV-1 infection diagnosis, this statistician notes whether a stopping boundary is reached that indicates that the relative cumulative rate of HIV-1 infection (RR, pooled mAb group/control) exceeds one. If the stopping boundary is met, then the unblinded statistician immediately informs the Chair of the DSMB and the Executive Secretary of the DSMB through secure communication procedures. As such, the potential harm monitoring is in real-time, with a result possible at any time, whereas in contrast the non-efficacy and high efficacy monitoring is conducted only at the 6-monthly scheduled DSMB meetings or at any extra DSMB meetings requested by the DSMB (with exception that the first non-efficacy analysis would be done and reported to the DSMB by secure means prior to a scheduled DSMB meeting if the 67th total primary endpoint event occurs prior to a non-efficacy analysis triggered by at least 45 endpoints by a scheduled DSMB meeting, as described in Table 3).

The potential harm monitoring is done using an exact one-sided binomial test of the null

hypothesis $H_0 : p \leq 2/3$ versus the alternative hypothesis $H_1 : p > 2/3$, where p is the probability that an HIV-1-infected participant was assigned to either of the two mAb groups (as compared to being assigned to the control group). The tests start at the 20th total infection through to the infection count at which the non-efficacy/high efficacy monitoring commences, which is a minimum of 45 and is a random variable that depends on the timing of DSMB meetings (this value is referred to as the n^{*th} infection). Based on protocol projections we assume that n^* is at most 67, which is useful for setting the critical values of the test. (If the highly unlikely result occurs that n^* exceeds 67, then the first non-efficacy analysis would be conducted based on 67 infections, which would serve the purpose of potential harm monitoring. The number 67 is chosen because that is the infection count at which a point estimate of zero PE would just correspond to an upper nominal 95% confidence bound for PE equal to 0.40; this approach to starting non-efficacy monitoring was suggested by Freidlin, Korn, and Gray (2010).) Each test is performed at a prespecified nominal/unadjusted alpha-level, which may vary over the multiple tests. The alpha-level used for each test is determined indirectly as follows: we must first choose the overall type I error rate we are willing to accept over the course of the monitoring (the overall probability that we reach a stopping boundary during the trial, when the mAb is actually safe, i.e., true $RR = 1$, equivalently $p = 2/3$); and secondly we must choose whether/how to vary the alpha-level from test-to-test. Using these pieces of information we determine the exact alpha-levels to be used for each test.

An overall 1-sided type I error rate of 0.05 is chosen for the family-wise error rate of the multiple hypothesis tests starting at the 20th HIV-1 infection endpoint through to the 67th. This type I error rate is chosen to balance the competing goals of participant safety and preventing false positive results. To prevent stopping too early, perhaps due to spurious results caused by wide sampling variability, stopping prior to the accumulation of 20 total infections was ruled out (the 2:1 mAb:control allocation ratio leads to this choice; in contrast a 1:1 allocation ratio would lead to starting at about 12 total infections). Table 4 shows the potential harm stopping boundaries in terms of the one-sided p-value cut-offs for a selected set of potential harm interim analyses starting at the 20th HIV-1 infection event.

9.2.2 Non-efficacy monitoring

For each AMP trial, the first non-efficacy analysis will be reported to the DSMB at the first scheduled 6-monthly meeting at which at least a total of 45 HIV-1 infection endpoints have occurred, combined over the three study groups. The analysis is based on all HIV-1 infection endpoints up until the time of data lock, and if this number exceeds 67, then the first non-efficacy analysis would be done based on 67 events and the report provided to the DSMB by secure means prior to the scheduled DSMB meeting (as noted above).

At each non-efficacy interim analysis PE is estimated with a 2-sided 95% nominal confidence interval using the same method as for the final analysis of PE described in Section 8.1. Based on projected accrual and HIV-1 incidence in the control groups it is expected that some participants will have reached the Week 80 study visit by the time of the first non-

Table 4: Potential harm monitoring stopping boundaries for each AMP trial: One-sided p-value cut-offs for rejecting $H_0 : p \leq 2/3$ in favor of $H_1 : p > 2/3$ with an exact 1-sided binomial test where p is the probability that an HIV-1-infected participant was assigned to one of the two mAb groups

No. of Infections in VRC01 Groups	No. of Infections in Control Groups	Per-Test Type I Error Rate (1-Sided P-value Cut-off)
20	0	0.003
20	1	0.013
20	2	0.018
22	3	0.018
25	4	0.018
28	5	0.018
31	6	0.018
34	7	0.018
37	8	0.018
40	9	0.018
43	10	0.018
45	11	0.018
48	12	0.018
54	13	0.018

efficacy interim analysis, such that PE, which is defined based on cumulative incidence of HIV-1 infection through to the Week 80 visit, can be estimated. At the early interim analyses, however, it is possible that no or very few participants will have reached the Week 80 study visit by the time of the analysis, precluding the ability to estimate PE. In this event, cumulative prevention efficacy through time t , $PE(t)$, will be estimated with fixed time point t chosen to be the latest possible time point where stable estimation can be achieved; this is operationalized by defining t as the maximum time point with available follow-up data from at least a total of 150 participants.

In all interim analyses of PE, participants with either event of CRF-confirmed study termination prior to study completion or 20 consecutive weeks without participant contact are right-censored at the time of occurrence of the first of these events. Twenty consecutive weeks represents two consecutive planned infusions, with 4 weeks of margin for variability in infusion visit windows.

The 2-sided 95% confidence intervals for PE, estimated in the same way as described for the final analysis, are reported for sequential monitoring of PE at every DSMB meeting through to the end of the trial.

9.2.2.1 Unblinded conditional power assessment at an interim analysis

Interim monitoring of PE for non-efficacy will be supplemented with an unblinded conditional power assessment. The estimation procedure will be similar to that described in Section 9.4.2 except (i) the blind-preserving “calculated control-group incidence under protocol assumptions on PE” (defined in Section 9.4.2) is replaced by the actual observed control-group incidence, and (ii) the following levels of PE in the future data are assumed: $PE = 0\%$, $PE = \widehat{PE}$ in the observed data, and $PE = 60\%$.

9.2.3 High efficacy monitoring

The 2-sided 95% confidence interval for PE used for non-efficacy monitoring is also used for high efficacy monitoring, where it is compared to $PE = 70\%$ instead of $PE = 40\%$ as a stopping boundary. High-efficacy monitoring is conducted at each interim analysis at which non-efficacy analysis is conducted.

9.2.4 Rationale for starting non-efficacy/high efficacy monitoring at at least 45 total infections

Freidlin, Korn, and Gray (2010) suggested beginning non-efficacy monitoring as soon as a point estimate of PE equal to zero would correspond to the nominal 95% confidence interval of a hazard ratio based efficacy parameter under a Cox proportional hazards model just barely ruling out the design alternative ($PE = 40\%$ in the AMP trials). This approach implies starting the non-efficacy monitoring at the 67th total infection in each AMP trial. However, based on protocol projections of accrual and incidence, between about 60 and 100 total HIV-1 infection events are expected in each trial, for PE varying over the range 0% to 60%. Therefore it would not be unlikely that no non-efficacy interim analysis would occur if the Freidlin, Korn, and Gray (2010) recommendation were strictly followed. Moreover, a high efficacy analysis would not occur, as its timing is synchronized to the non-efficacy monitoring timing, which could be problematic if the PE is very high. Accordingly, the monitoring starts at at least 45 infections, which is judged to be large enough to have reasonable precision and small enough to make it likely that some non-efficacy/high efficacy interim analyses would occur during the trial. Note that if the first non-efficacy interim analysis occurred at 45 total infections, then stopping for non-efficacy, which would occur if the nominal 2-sided 95% confidence interval lies below 40%, would correspond to a negative PE estimate. This is an advantageous property in that a result of early non-efficacy would be an unambiguous result about absence of prevention efficacy.

9.3 Monitoring of the Use of PrEP

The use of oral FTC/TDF as PrEP (either off-study or provided in the study) may impact study outcomes (e.g., by lowering HIV-1 incidence rendering a loss of study power). Dried blood spot (DBS) samples will be used for assessment of quantitative concentrations of intracellular TFV-DP.

Prevalence of oral FTC/TDF will be reported both as any detectable use and estimated effective use. Estimated percentages of person-years at-risk during any detectable FTC/TDF use and during inferred effective FTC/TDF use will be reported. We summarize how inferred effective use is measured. Current knowledge about PrEP in MSM indicates consistent use of at least 4 doses a week is required to achieve substantial levels of protection. The lower quartile of simulated tenofovir diphosphate (TFV-DP) levels in DBS at 4 doses per week is 719 fmol/punch (Castillo-Mancilla et al., 2013). In iPrEx OLE, the protective levels of TFV-DP in DBS were quantified as 700 fmol/punch (Grant et al., 2014), that is, there were no infections at visits where TFV-DP concentration was 700 fmol per punch or greater. Current knowledge about PrEP in women indicates consistent use of 6–7 doses a week is required to achieve protection. The lower quartile of simulated TFV-DP levels in DBS at 6 doses per week is 1064 fmol/punch (Castillo-Mancilla et al., 2013). In the HVTN 704/HPTN 085 study we will use 700 fmol/punch as the cut-off to define effective PrEP use based on the lower quartile cited above. For the HVTN 703/HPTN 081 study we will use 1,000 fmol/punch since current knowledge suggests that at least 6 doses of PrEP per week is required for effective PrEP use in women based similarly on the lower quartile. Ongoing work with calibration of DBS from directly observed dosing studies may refine these thresholds. PrEP use measures will be reported by arm to the DSMB; in addition both the OC and the protocol team leadership will see pooled estimates of FTC/TDF use.

HVTN 704/HPTN 085 collects and stores DBS samples at every study visit, whereas HVTN 703/HPTN 081 collects and stores DBS samples at pre-specified DBS sample collection days. The sample collection days can vary by study site; however, it is expected that the collection days will occur once per month. Furthermore, in order to tune the precision of PrEP use estimation, the frequency of collection may be increased. While the storage and collection differs by protocol, the selection of stored samples to assay will be similar. We refer to the method of selecting participant samples for assaying DBS samples for prospective monitoring of PrEP as the DBS sampling plan.

At a given calendar time T (e.g., a fixed date prior to a scheduled DSMB meeting), we are interested in the population-level parameter, percent person-years at-risk for HIV on effective PrEP use between initiation of DBS storage, and time T . Definition of this parameter makes the assumption that we have an assay readout from stored samples that accurately measures effective PrEP use as a binary outcome at the time the sample was drawn; importantly it does not require an accurate measurement of effective PrEP use the day before or for any period of time earlier than the sampling day. In addition to estimating percent person-years on effective PrEP use we define a similar parameter, percent person-years exposed to

detectable PrEP using the lower limit of quantitation (LLOQ) of the DBS assay.

Define the target parameter of interest as

$$\Phi(T) = \frac{\int_{T_0}^T p(t) E[Y(t)] dt}{\int_{T_0}^T E[Y(t)] dt}$$

where T_0 is the time since the first person enrolled after DBS storage commenced, $p(t)$ is the percent of participants on effective PrEP use at time $t \in [T_0, T]$, and $E[Y(t)]$ is the expected number of participants with DBS storage at-risk for HIV at time t .

We estimate $\Phi(T)$ based on the binary PrEP use readout from the DBS assay and the DBS sampling plan. Let i ranging from 1 to N index study participants and let j ranging from 1 to M_i index participant serum collection dates that are sampled for assaying. For each sample collected, we have an indicator x_{ij} of effective PrEP use which is only measured if the DBS sampling indicator, Δ_{ij} , is equal to 1. The estimated percent person-years on effective PrEP use from the initiation of PrEP monitoring time T_0 until time T is defined as

$$\hat{\Phi}(T) = \frac{\sum_{i=1}^N \sum_{j=1}^{M_i} \Delta_{ij} x_{ij} \pi_{ij}^{-1} P_{ij}}{\sum_{i=1}^N \sum_{j=1}^{M_i} P_{ij}}$$

where the sampling probability, π_{ij} , and person-years, P_{ij} , are defined below.

Let k ranging from 1 to K index the DBS sampling plan collection intervals $[T_0, T_1]$, $(T_1, T_2]$, $\dots$, $(T_{K-1}, T_K]$ where the right endpoint of each interval is a sample collection date (with $T_K \equiv T$) and define $\mathcal{T}_k$ as the k^{th} interval. Let $t_{i1} < t_{i2} < \dots < t_{iM_i}$ be the sampling times in $[T_0, T]$ for the i^{th} participant and define t_{i0} as the maximum of T_0 and the i^{th} participants enrollment time. The DBS sampling plan determines which samples, collectively across participants, will be assayed for PrEP use. Define the set of samples, S_{ij} , as all samples collected during the same collection interval $\mathcal{T}_k$ as the sample i, j . That is, $S_{ij} \equiv \{i', j' | t_{i'j'} \in \mathcal{T}_k \text{ for } k \text{ s.t. } t_{ij} \in \mathcal{T}_k\}$. Define the sampling probability as

$$\pi_{ij} \equiv \frac{\sum_{i', j' \in S_{ij}} \Delta_{i'j'}}{|S_{ij}|}$$

where $|S_{ij}|$ is the number of samples in set S_{ij} . Define person-years, P_{ij} , as $t_{ij} - t_{i(j-1)}$. Note that our parameter of interest can be defined and estimated for the entire study cohort, as well as for sub-regions (e.g., North America for the HVTN 704/HPTN 085 study). We will report bootstrap 95% confidence intervals for $\Phi(T)$.

The same approach is used for point and confidence interval estimation of the percent person-years exposed to detectable PrEP use.

An example of PrEP use report statistics are shown in Table 5.

Table 5: Estimated rates of PrEP use and estimated percent person-years on effective PrEP use

Number of DBS specimens collected over the 1 st batch period	N_1
Number of DBS specimens assayed over the 1 st batch period	N_2
Proportion of assayed specimens with TFV-DP above LLOQ (95% CI)	N_3/N_2 (x.xx, x.xx)
Proportion of assayed specimens with TFV-DP above effective use threshold* (95% CI)	N_4/N_2 (x.xx, x.xx)
Percent person years on detectable PrEP through date T=xx (95% CI) [#]	$\widehat{\Phi}(T)_d$ (x.xx, x.xx)
Percent person years on effective PrEP through date T=xx (95% CI) [#]	$\widehat{\Phi}(T)_e$ (x.xx, x.xx)
Repeat through N th batch period	

*threshold defined by study (700 fmol/punch MSM+TG, 1000 fmol/punch sub-Saharan African Women)

[#] $\widehat{\Phi}(T)_d$ is an estimate of the target parameter of interest based on measured TFV-DP above the LLOQ.

Similarly, $\widehat{\Phi}(T)_e$ is based on TFV-DP above the study specific threshold for effective PrEP use.

9.3.1 Simulation Study for PrEP Monitoring

In order to determine the number of DBS samples that should be collected and assayed a simulation study was run. For a simulated AMP trial, the PrEP monitoring plan was implemented based on the following assumptions: 1) Enrollment falls randomly between Monday and Friday; 2) Follow-up visits follow the visit schedule exactly; 3) Missed visits are distributed uniformly at a rate of 10%; 4) Dropout is 10% per person year based on an exponential distribution; 5) HIV-infection is 3% for HVTN 704/HPTN 085 (or 5.5% for HVTN 703/HPTN 081) per person year based on an exponential distribution; and, 6) Initiation of DBS sample collection begins as of November 1, 2016 in both protocols. PrEP use was simulated at various constant rates among trial participants and participants are assumed to be either on (or off) PrEP during the entire trial. Simulation results for each trial are presented for the number of samples collected spaced at 6 month intervals. The intervals are spaced such that the last collection time point is approximately 3.5 months prior to the next DSMB meeting to allow the intracellular TFV-DP assay to be run and a report generated. In this simulation, all samples collected per protocol HVTN703/HPTN081 version 2.0 would be assayed. For the HVTN704/HPTN085 trial, all samples collected the clinic business day closest to the 15th of each month would be assayed. Simulation results are shown in Figures 2 and 1.

The simulation study results show that by the time 200 samples have been selected the confidence intervals around the estimate of PrEP use are reasonably tight and by the time 500 samples have been selected the extra gain in precision as more samples are assayed becomes limited. However, continuing to assay samples over the course of the trial will allow estimation of temporal trends in PrEP use. The simulation also shows that when PrEP prevalence is very low the bootstrap confidence interval is unlikely to provide proper coverage.

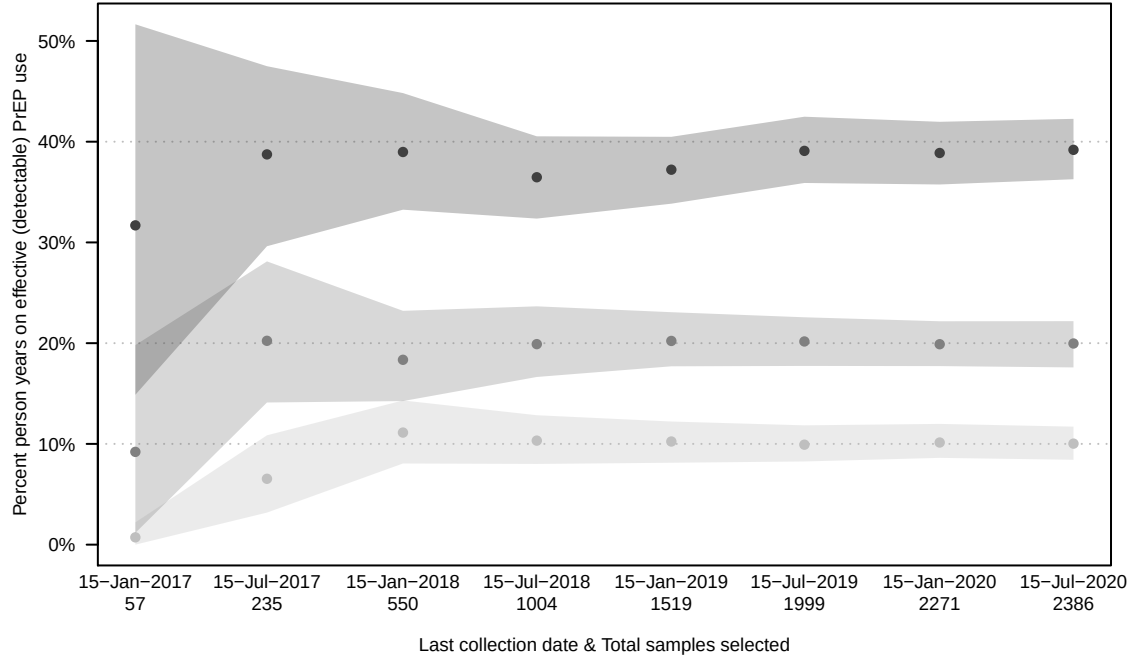


Figure 1: PrEP use Monitoring under three PrEP use scenarios (40%, 20% and 10% per person year) in the HVTN704/085 trial. For 6-monthly intervals shown on the x-axis all samples assayed to date are used to estimate PrEP use prevalence from the beginning of monitoring until that time using the estimator described in Section 8.3. Below each date is the total number of samples that would be assayed according to the simulation study. Estimates are shown as a dots of varying color intensity corresponding to the three PrEP use scenarios. Corresponding color bands are used to show the 95% bootstrap confidence interval for each estimate.

9.4 Monitoring for Futility to Assess PE

The DSMB monitors the trial for futility to assess PE defined as overly slow progress toward the Target Number of Infections (defined below) or insufficient conditional power for the primary analysis given the observed data. Six-monthly DSMB meetings will be held for monitoring for futility to assess PE, synchronized with interim analyses of PE.

For each AMP trial, we define the Target Number of Infections to be the number of primary endpoints after Week 0 and by the Week 80 visit such that the trial has approximately 70% power to reject $H_0 : PE \leq 0\%$ if $PE = 60\%$ (using a 1-sided 0.025-level cumulative hazard-based Wald test). This number is about 29, calculated based on simulated trials described in the protocol. We define the Time to the Target Number of Infections (TTNI) to be the number of months from the time of the first enrolled participant until the Target

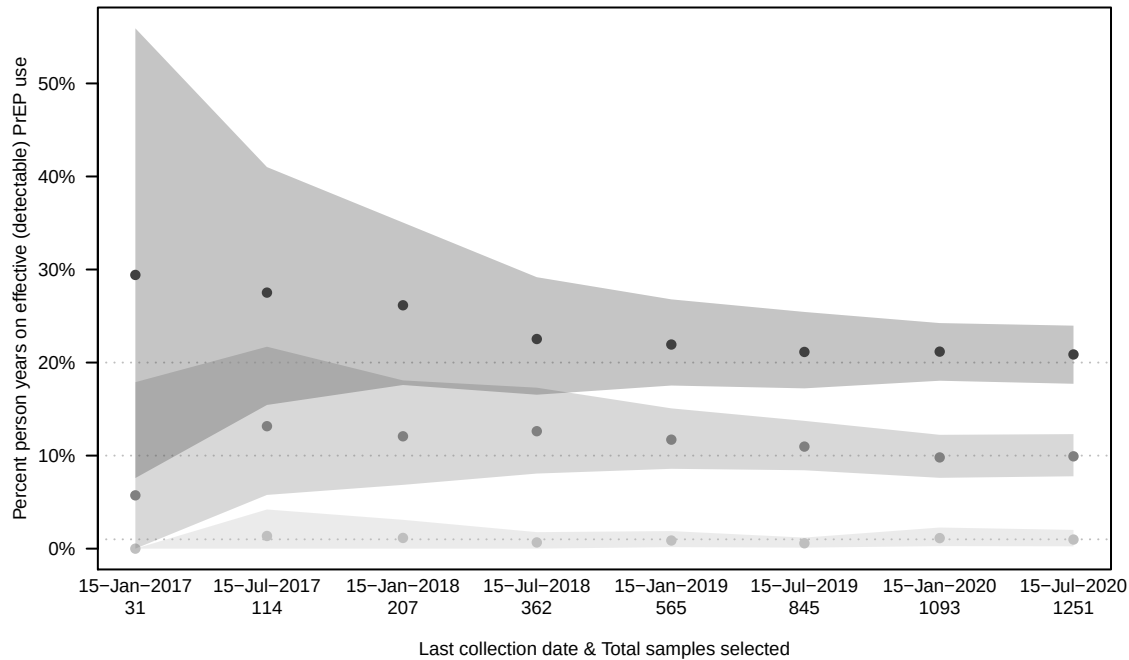


Figure 2: PrEP use Monitoring under three PrEP use scenarios (20%, 10% and 1% per person year) in the HVTN703/081 trial. For 6-monthly intervals shown on the x-axis all samples assayed to date are used to estimate PrEP use prevalence from the beginning of monitoring until that time using the estimator described in Section 8.3. Below each date is the total number of samples that would be assayed according to the simulation study. Estimates are shown as a dots of varying color intensity corresponding to the three PrEP use scenarios. Corresponding color bands are used to show the 95% bootstrap confidence interval for each estimate.

Number of Infections. The objective of the futility to assess PE monitoring, conducted for each AMP trial, is to provide to the DSMB and the OC periodic projections of the estimated distribution of the TTNI. If the probability of reaching the TTNI within a specified time frame is too low, then a guideline would be met for recommending completing the trial based on the inability to answer the primary PE question in a timely manner. While it is the primary responsibility of the OC to make decisions regarding trial operations and closure based on the monitoring for futility to assess PE, because it is primarily a resource issue, issues of scientific integrity could also be involved, such that DSMB review and input is warranted. The monitoring for futility to assess PE will be provided to the DSMB as part of the closed DSMB report, which will then be provided to the OC as a stand-alone report immediately after the closed session.

The projections of the TTNI will be provided to the DSMB at each 6-monthly DSMB meeting

starting at the meeting taking place at least 12 months after the first volunteer is enrolled. This calculation will use the observed recruitment, HIV-1 incidence, and retention rates. For the Americas/European trial, the sample size calculations assume 30 months of enrollment and 80 weeks of total follow-up per participant for monitoring for primary HIV-1 infection endpoints, constituting $30 + 18.46$ months = 48.46 months. For the sub-Saharan Africa trial, the sample size calculations assume 32 months of enrollment and 80 weeks of total follow-up per participant for monitoring for primary HIV-1 infection endpoints, constituting $32 + 18.46$ months = 50.46 months. If the projected TTNI for a trial reliably exceeds 48.46 (or 50.46) months after trial opening, then the DSMB may consider recommending maneuvers to reduce this waiting time. In particular, if continued recruitment could reduce the projected TTNI by more than 3 months, sites (or selected sites with relatively high recruitment rates) would be expected to extend recruitment for up to 6 months. If the projected TTNI reliably exceeds 60 months (5 years) after appropriate attempted remediation, then the OC would consider recommending termination of the trial under consideration. In the event that the trial under consideration is terminated, then at that time the final analysis would be performed.

At each 6-monthly DSMB meeting, blinded conditional power calculations will also be provided. Importantly, these power calculations only utilize interim data pooled over the three study groups in order to maintain trial integrity. Blinded conditional power is defined as power to reject $H_0 : PE \leq 0\%$ assuming $PE = 60\%$ and given actual enrollment and study-arm-pooled dropout and HIV-1 incidence data from trial start through the time of the interim analysis. An estimate of conditional power that is below 50% constitutes an additional guideline for futility to assess PE.

9.4.1 Calculation of the projected time to the target number of infections at an interim analysis

The method for projecting the TTNI for each trial is based on the following approach to simulating efficacy trials. A similar process was used for HVTN 505. The trial is modeled as a combination of three processes—enrollment, dropout, and HIV-1 infection—and a large number of trials is simulated. The three processes are assumed independent and their distributions are taken to be Poisson, exponential, and exponential, respectively. Data are generated at the level of the individual participant, such that for each participant we obtain an enrollment time, an (underlying true) infection time, and a dropout time. Only the minimum of the infection and dropout times is observable, and the average value for this minimum is beyond the duration of the trial, such that neither event will be observed for most participants. In the absence of observed trial data, the parameters for the enrollment, infection, and dropout processes are chosen to match our pre-trial assumptions regarding these rates:

- enrollment rate: 10.19 participants per week in weeks 1–13; 20.38 participants per week in weeks 14–139 [MSM/TG trial HVTN 704/HPTN 085]; 6.07 participants per week in

weeks 1–13; 12.15 participants per week in weeks 14–130 [sub-Saharan African women trial HVTN 703/HPTN 081]

- dropout rate: 0.10 dropouts/person-year [both trials]
- infection rate: 0.03 infections/person-year [MSM/TG trial]; 0.055 infections/person-year [sub-Saharan African women trial]

The first step in simulating each trial is to enroll a certain number of participants per week according to a random draw from a Poisson distribution with the rate parameter as listed above. Enrollment continues week-by-week until a total of 2700 or 1500 participants is reached. Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. Following enrollment, the infection and dropout times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider dropout events to have occurred at the dropout time (in days) that was generated (assuming it was less than the infection time). For participants who become HIV-1-infected, we record their time of diagnosis as the time of the first study visit following the true infection time. It is this time of diagnosis that we observe for infected participants.

Once all participants have had their enrollment and infection/dropout times generated and (if necessary) infection diagnosis time determined, we can then obtain the TTNI for the simulated trial. For participants with HIV-1 infection diagnosis, we add their enrollment and infection diagnosis times together to obtain diagnosis times that are relative to the beginning of the study (in calendar time) rather than in relation to their own enrollment times. Finally, we order these participants by these new infection diagnosis times, from smallest to largest, and identify the 29th one from the beginning. The TTNI is this 29th infection diagnosis time after Week 0 by the Week 80 visit.

A modification of the above procedure for simulating an efficacy trial is used for predicting the TTNI at a given interim analysis for each AMP trial. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on pre-trial assumptions. In particular:

- enrollment rate: estimated based on the rate observed thus far in the study
- dropout rate: estimated based on the rate observed thus far in the study
- infection rate: estimated based on a posterior distribution for the infection rate formed by combining the observed data with our prior belief about the infection rate based on the pre-trial assumptions.

A new value for the infection rate is sampled from the posterior distribution for each simulated trial. The rationale for this approach is to help stabilize the infection rate early in the

trial, when insufficient time will have passed to accrue many infections. If we were to rely solely on the observed infections, we might by chance obtain a very low rate, which would lead to an unrealistic prediction of the TTNI. The effect of the prior is highest early in the trial, when we have the least data, and is gradually reduced as more trial data accumulate. By the year-2 interim analysis, the prior has little effect. We use a gamma distribution prior (which is conjugate to the exponential used for the infection rate), with parameters chosen so that the prior mean matches the pre-trial assumption for the infection rate and with information content approximately equivalent to what is expected in the first 12 months of the study.

At a given interim analysis, the TTNI is estimated based on simulating 100,000 trials using the above procedure, each of which yields a predicted TTNI. The projected TTNI is the median predicted TTNI over the 100,000 trials. As noted earlier, the guideline for declaring futility to assess PE is that the projected TTNI lies reliably above 5 years, which translates into an operational requirement that at least 75% of the 100,000 predicted TTNI values be greater than 5 years (i.e., the probability that the true TTNI is greater than 5 years is at least 0.75).

The DSMB reports include boxplots of the TTNI across the 100,000 trials. Figures on dropout over time, HIV-1 incidence, and enrollment (described in Appendix A Figures 1, 14 and 17) are also included to aid interpretation of the results.

9.4.2 Blinded conditional power assessment at an interim analysis

This conditional power assessment aims to preserve blinding of the OC and treatment-blinded statisticians and proceeds as follows: first, we estimate the overall primary endpoint incidence in the observed data, pooling over the three study groups. Second, assuming that incidence-based $PE = 60\%$, the control-group endpoint incidence that would yield this overall endpoint incidence is calculated; we call this the “calculated control-group incidence under protocol assumptions on PE.” Third, 10^5 trials are simulated using the above procedure where the uncertainty in estimation of the control-group incidence is accounted for by drawing from the posterior distribution of the control-group endpoint incidence combining the calculated control-group incidence under protocol assumptions on PE with the protocol-assumed annual control-group incidence of 3.0% in the MSM/TG trial or 5.5% in the sub-Saharan African women trial. Given the assumption that incidence-based $PE = 60\%$ in the future data, blinded conditional power is estimated as the proportion of simulated trials in which $H_0 : PE \leq 0\%$ is rejected using a one-sided 0.025-level Wald test of the equality of log cumulative hazard functions at 80 weeks for the pooled mAb group and the control group. While the testing procedure accounts for the interim monitoring of PE for potential harm, non-efficacy, and high efficacy, the critical value of the Wald test is not adjusted for this interim monitoring; the rationale for using a monitoring-unadjusted critical value is provided in Section 8.1.

9.5 Operational Analysis Near the End of Enrollment to Decide whether to Consider Expanding Enrollment

After each DSMB meeting that included reporting of futility to assess PE, the OC will receive the results of the futility analysis. The OC will also be provided additional information at the time of a special DSMB meeting scheduled to take place approximately 3 months before the completion of enrollment, based on ongoing projections of time until full enrollment by the study statisticians. For this meeting, study statisticians will prepare a report that includes the calculations typically in a futility to assess PE analysis, along with additional guidance as to whether the HIV-1 incidence pooled over treatment groups is “too low” or “acceptable” to sufficiently power the study. The report will be shared both with the DSMB and with the OC. The OC will then have the opportunity to decide whether, if incidence is lower than anticipated but not so low that futility to assess PE is declared, to expand enrollment beyond the originally planned 2700 or 1500, in order to maintain the ability of the study to meet the study’s primary objectives. The meeting will be timed before but near to the end of enrollment to allow a potential decision to expand enrollment to occur before the enrollment apparatus is scaled down, while also allowing the decision to be made on the maximal amount of primary endpoint infections. The OC may also be presented information on the degrees of enrollment expansion that would be required in order to achieve blinded-conditional power and infection-arm-pooled infection totals at various levels.

9.6 Monitoring for Performance Standards of Quality of Trial Conduct

The protocol team and study investigators will have performance standards regarding the quality of trial conduct in addition to the study endpoint rate. Some of these use standard metrics detailed in the Network Evaluation Metrics and Standards document, whereas others are specific to the AMP trials. Some of these standards will relate to achievement of targeted levels of:

1. participant enrollment into the trial (targets based on protocol assumptions);
2. retention of participants (target 5% annual dropout or less, with minimally acceptable level of no more than 10% annual dropout; also target 90% visit attendance among participants under follow-up [NEC standard]).
3. adherence to receipt of infusions (target 90% of infusions received, with minimally acceptable level of 70% of infusions received).
4. quality and timeliness of HIV-1 diagnostic testing.
5. quality and timeliness of data collected on case report forms.

Appendix A describes the output that is used to evaluate items 1 (Figure 17), 2 (Table 5A and Figure 1), and 3 (Table 5B and Figure 3), and Section 9.1 provides additional information about 3 in terms of the feasibility check monitoring.

9.6.1 Expanded details for reporting on item 4: quality and timeliness of HIV-1 diagnostic testing

1. **Timeliness:** Turnaround time from blood collection to diagnostic reporting is summarized. This process monitors the site, the site-processing lab, the shipping company and the actual diagnostics lab. In addition the turnaround time from arrival in the lab to reporting is monitored, which isolates the turnaround time to the lab.
2. **Quality:** No additional monitoring for HIV-1 diagnostic quality is done beyond the fact that the labs participate in CAP and VQA and they are all audited annually by DAIDS.

9.6.2 Expanded details for reporting on item 5: quality and timeliness of data collected on case report forms

This reporting will use NEC standard metrics, as detailed in the Network Evaluation Metrics and Standards document (pages 12-14). In summary, the reporting outputs are as follows:

1. **For Quality:** For **QC Rate**, the standard metric for satisfactory quality is < 10 QCs per 100 pages. The denominator for this metric includes the total number of pages entered in the database during the time period. For refaxes, only the most recent page faxed is included. All CRF pages faxed to SCHARP are included in this calculation. Total CRF pages are labeled (Total Pages1) in the DMQ table.
For **QC Resolution**, the standard metric is $> 80\%$ of QCs resolved in < 7 calendar days.
For **Percent EDCd**, note that quality tends to be higher when pages are submitted via EDC (real time validation, faster submissions, etc), and this metric incentivizes sites to use EDC.
2. **Timeliness:** The standard metric for CRF Submission Rate (% pages faxed/EDCd on time) is $> 90\%$ of pages submitted within < 4 calendar days. The denominator for this metric is not total pages, as it excludes pages that, according to study operations, may not be completed and/or faxed immediately following a study visit (e.g., screening visit forms). Log-based forms are also not included. For refaxes, only the initial page faxed is included. Only time-critical CRF forms are calculated. Screening and log based forms are excluded. CRFs included in this calculation are labeled (Total Pages2). HIV test results are excluded.

The DSMB and the leadership of the AMP trials will monitor whether the trials are achieving at least minimally acceptable levels of key performance standards. The DSMB will make recommendations to improve areas that are deficient. Termination of a trial would be considered if it appears unlikely that minimally acceptable performance will be achieved.

10 Statistical Software

All analyses described in this SAP will be conducted in *R*.

11 Roles of Study Statisticians

HVTN SDMC statisticians will be blinded or unblinded to treatment group. During protocol development and after primary follow-up is completed, there will be no distinction between the roles; both types of statisticians will be responsible for designing and analyzing the study. During the primary follow-up period, however, only the treatment-unblinded statistician(s) will see interim data broken down by treatment group. Their role will be to conduct the interim monitoring and to produce and present reports on accruing data to the study DSMB. During the primary follow-up period, treatment-blinded statisticians will see only the interim data pooled across study groups. This way, treatment-blinded statisticians can assist protocol leadership in making decisions about modifications to the protocol without being influenced by interim efficacy results.

Appendix A

Mock tables and figures for the DSMB Closed Report are included below. The Closed Report summarizes trial information pooled across the treatment groups (labeled Total) and by masked treatment assignment (labeled A, B, and C). At the request of the DSMB, protocol statisticians will unmask treatment labels. A subset of these tables and figures will form the Open Report, in which trial information is reported pooled across the treatment groups.

DRAFT

HVTN xxx/ HPTN xxx

**Data and Safety Monitoring Board (DSMB)
CLOSED Report**

Tables and Figures

Table 1. Disposition of Study Participants by Treatment Assignment
Table 2. Baseline Participant Characteristics by Treatment Assignment
Table 3. Baseline Risk Behaviors by Treatment Assignment
Table 4. Study Status and Reasons for Early Study Termination by Treatment Assignment
Table 5A. Visit Retention by Treatment Assignment
Table 5B. Adherence by Treatment Assignment
Table 6. Permanent Discontinuation of Infusions by Treatment Assignment
Figure 1. Study Continuation (Time to Discontinuation) by Treatment Assignment
Figure 2. Boxplot for Time Between Infusions by Treatment Assignment
Figure 3. Sample of Adherence Patterns over Study Time by Treatment Assignment
Table 7A. Maximum Local Reactogenicity Summary by Treatment Assignment
Table 7B. Maximum Systemic Reactogenicity Summary by Treatment Assignment
Figure 4. Maximum Local Reactogenicity, by Treatment Assignment
Figure 5: Maximum Systemic Reactogenicity, by Treatment Assignment
Table 8. Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC) Listed by Treatment Assignment, Participant and Decreasing Severity
Table 9. Adverse Events (AEs) by System Organ Class and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 10. Grade 3–5 Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 11. Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 12. Adverse Events (AEs) Related to Study Product by High Level Term and Treatment Assignment
Table 13A. Distribution of Safety Laboratory Values, by Treatment Assignment
Table 13B. Safety Laboratory Values Meeting Grade 1 AE Criteria or Above, by Treatment Assignment
Table 14. Pregnancy Listing
Figure 6. Boxplot for ALT by Infusion Visit and Treatment Assignment
Figure 7. Boxplot for Hemoglobin by Infusion Visit and Treatment Assignment

Figure 8. Boxplot for Platelets by Infusion Visit and Treatment Assignment
Figure 9. Boxplot for WBC by Infusion Visit and Treatment Assignment
Figure 10. Boxplot for Neutrophil Count by Infusion Visit and Treatment Assignment
Figure 11. Boxplot for Lymphocyte Count by Infusion Visit and Treatment Assignment
Figure 12. Boxplot for Creatinine by Infusion Visit and Treatment Assignment
Figure 13. Confirmation/Adjudication Process for HIV Infections
Table 15. HIV Adjudication Timeline
Table 16. HIV Infections
Figure 14. Cumulative HIV Incidence Among All MITT Participants by Treatment Arm
Table 17. ART Initiation among MITT Infected Participants
Figure 15. Viral Load Over Time Among All Infected MITT Participants
Figure 16. Cumulative Number of Infusions Missed by Infusion Visit for All Infected MITT Participants
Table 18a. Visit Retention for All MITT Pre-Trial HIV-1 and HIV-2 Infected Participants by Treatment Assignment
Table 18b. Visit Retention for All MITT Post-Trial HIV-1 Infected Participants by Treatment Assignment
Figure 17. Cumulative Enrollment

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 1. Disposition of Study Participants by Treatment Assignment^

	Total	A	B	C
Number Randomized	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pending Enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number Enrolled*	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
On Study (in Primary Follow-Up)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Primary Follow-up	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Study Termination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

^ Enrolled implies receipt of the first study product

* Primary Follow-Up is 92 weeks for uninfected participants and 24-weeks post-diagnosis for infected participants

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 2. Baseline Participant Characteristics by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Gender Identity				
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Queer	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Age (years)				
18 - 20	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
21 - 30	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
31 - 40	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
41 - 50	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median	xx	Xx	xx	xx
Min, Max	xx - xx	xx – xx	xx - xx	xx - xx
Race				
White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Black or African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Asian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Hawaiian/Pacific Islander	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Native Am./Alaska Native	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other Race	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Multi-racial	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

NOTE: Participants may self-report more than 1 gender identity, thus numbers and percentages may total to more than 100%

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Number Sex Partners in the Last Month				
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median	xxx	xxx	xxx	xxx
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Had an HIV+ Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Receptive Vaginal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Insertive Vaginal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Insertive Anal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Receptive Anal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Alcohol Use				
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Monthly or less	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2-4 times a month	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2-3 times a week	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
4 or more times a week	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Prefer not to answer				
Injection Drug Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Marijuana Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Crack cocaine use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Powder cocaine use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Amphetamine/Methamphetamine/Crystal Meth Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Methaqualone or Mandrax Use?				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Heroin, Prescription Pain Killers/Medications Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
MDMA or Ecstasy Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Popper Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 4. Study Status and Reasons for Early Study Termination by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Status				
In Infusion Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
In FU, Completed Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
In FU, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed FU and Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed FU, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination, Completed Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons for Early Termination	(n=x)	(n=x)	(n=x)	(n=x)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant refused	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to adhere to visit schedule	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant relocated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to contact	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Investigator decision	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Inappropriate enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duplicate screening/enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early study closure	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant incarcerated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Study product infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination Due to an Adverse Experience	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination Due to Study Product infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 5A. Visit Retention by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx	xxx	xxx	xxx
Week 4 / 28 days post Infusion 1				
Expected and/or Completed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently discontinued infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				
Week 92 / 140 days Post Infusion 10				
Expected and/or Completed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently discontinued infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Post-infusion visits are not expected if the infusion visit was not done.

Retention = # Participants who completed the visit / # Participants expected for and/or completed the visit.

A visit is considered expected if the participant is in Schedule 1 at the time of the visit and the visit window has closed.

A visit is considered completed once the Post-Enrollment IV Infusion Administration or Specimen Collection form is entered in the study database.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 5B. Infusion Adherence by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx	xxx	xxx	xxx
Week 0 / Infusion 1				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 8 / Infusion 2				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
Week 72 / Infusion 10				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Retained = # Participants who completed the visit

A visit is considered completed once the Post-Enrollment IV Infusion Administration or Specimen Collection form is entered in the study database

A participant has received infusion once the Post-Enrollment IV Infusion Administration is entered in the study database

.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

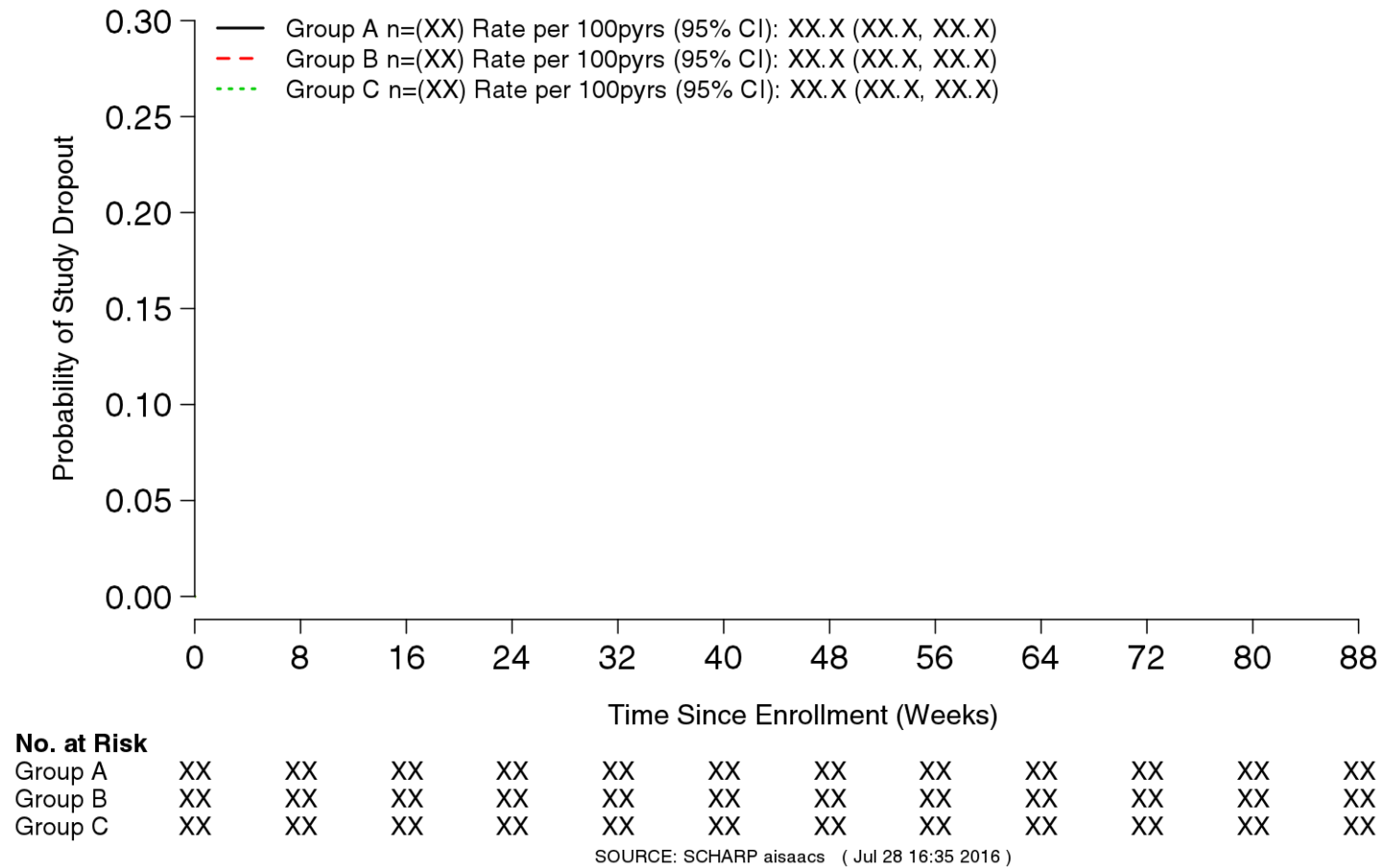
Data Cutoff date:[Date].

Table 6. Permanent Discontinuation of Infusions by Treatment Assignment

	Total	A	B	C
Infusion Status				
In Infusion Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Infusions Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons For Discontinuation	xxx	xxx	xxx	xxx
Pregnancy	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
HIV infection	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Clinical event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reactogenicity symptom	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Investigator reason	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant refused study product infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Co-enrollment in a study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Two reactive HIV tests	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

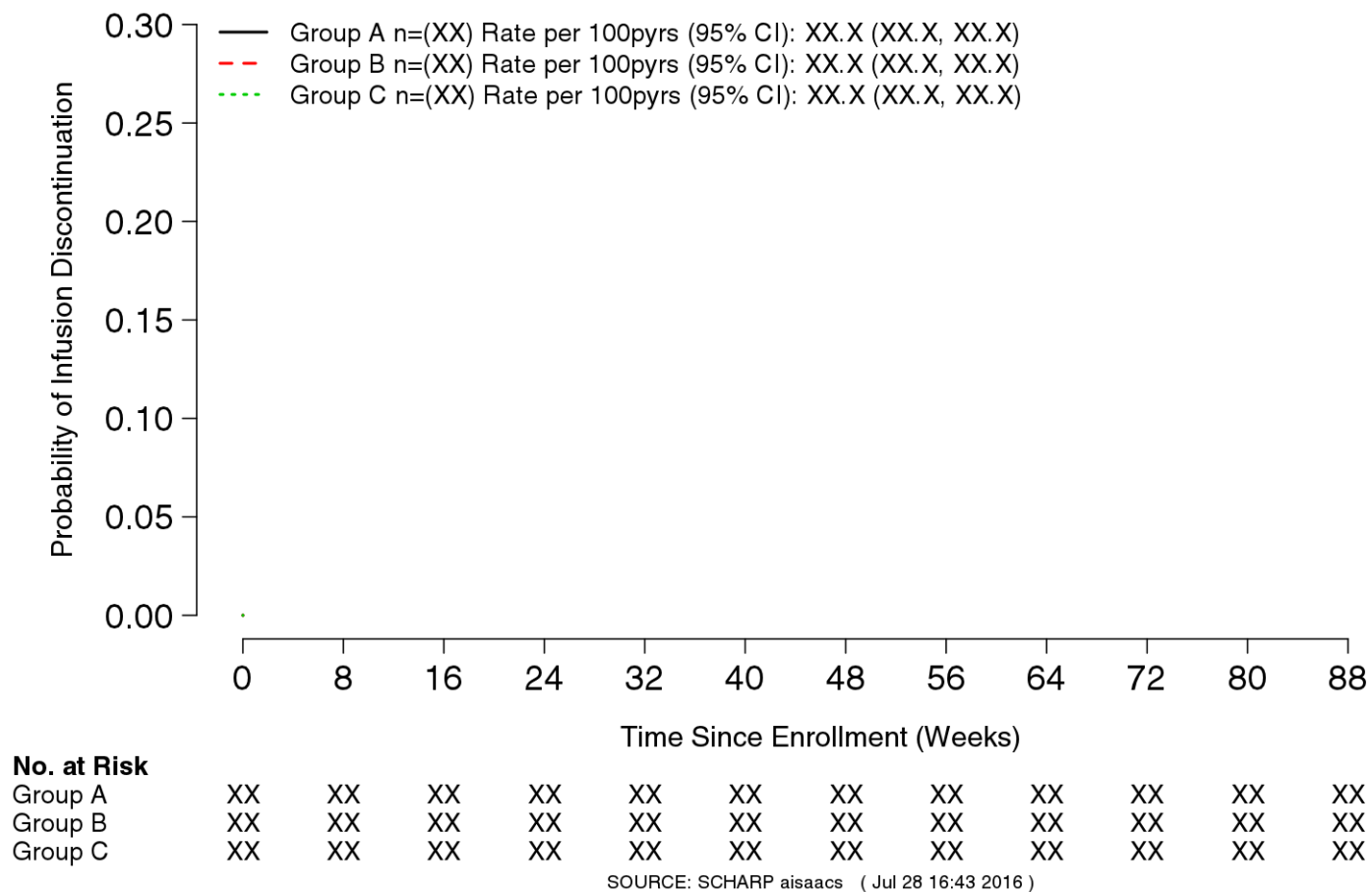
HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 1A. Cumulative Incidence of Dropout by Treatment Assignment



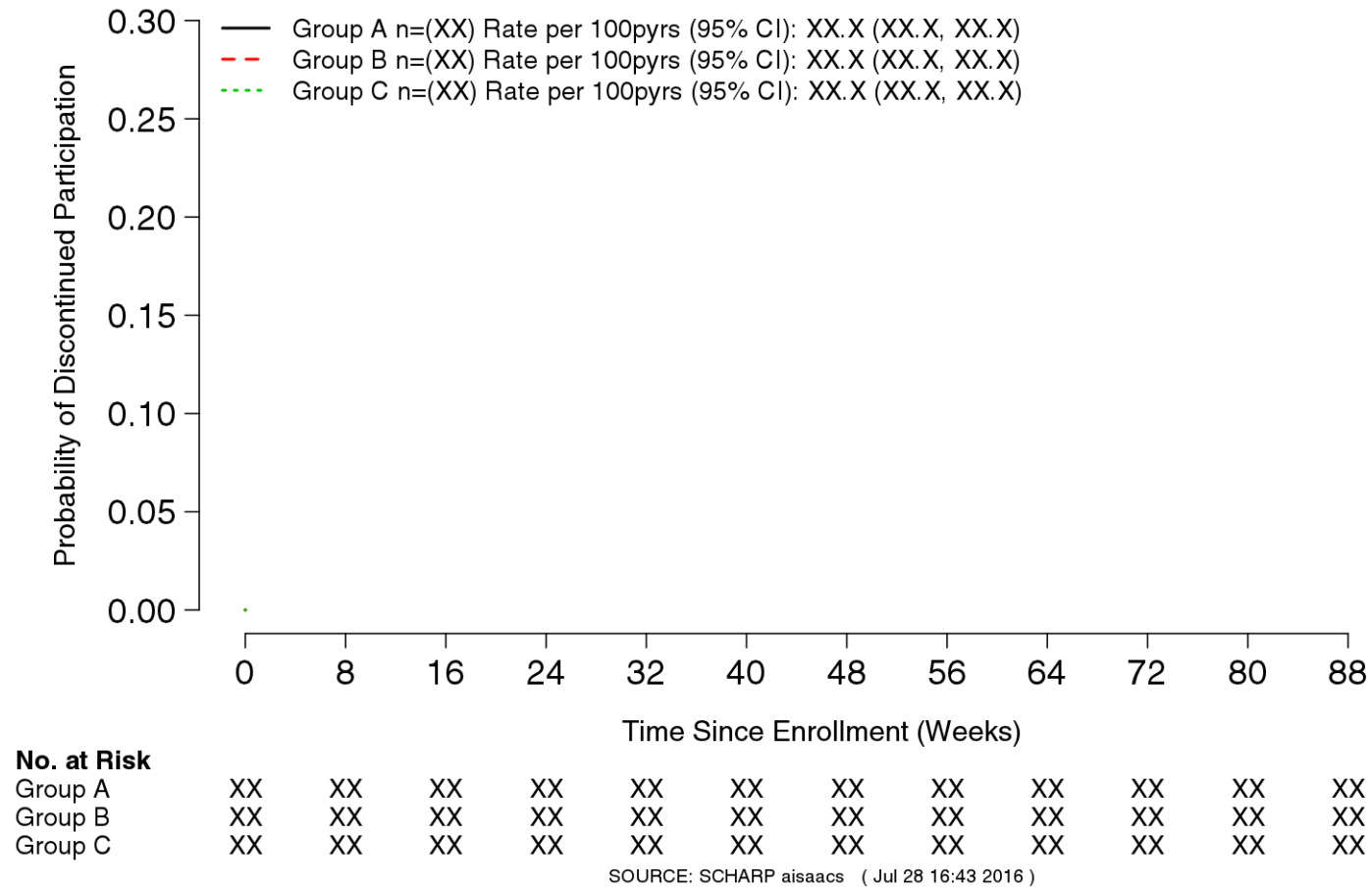
HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 1B. Cumulative Incidence of Infusion Discontinuation by Treatment Assignment



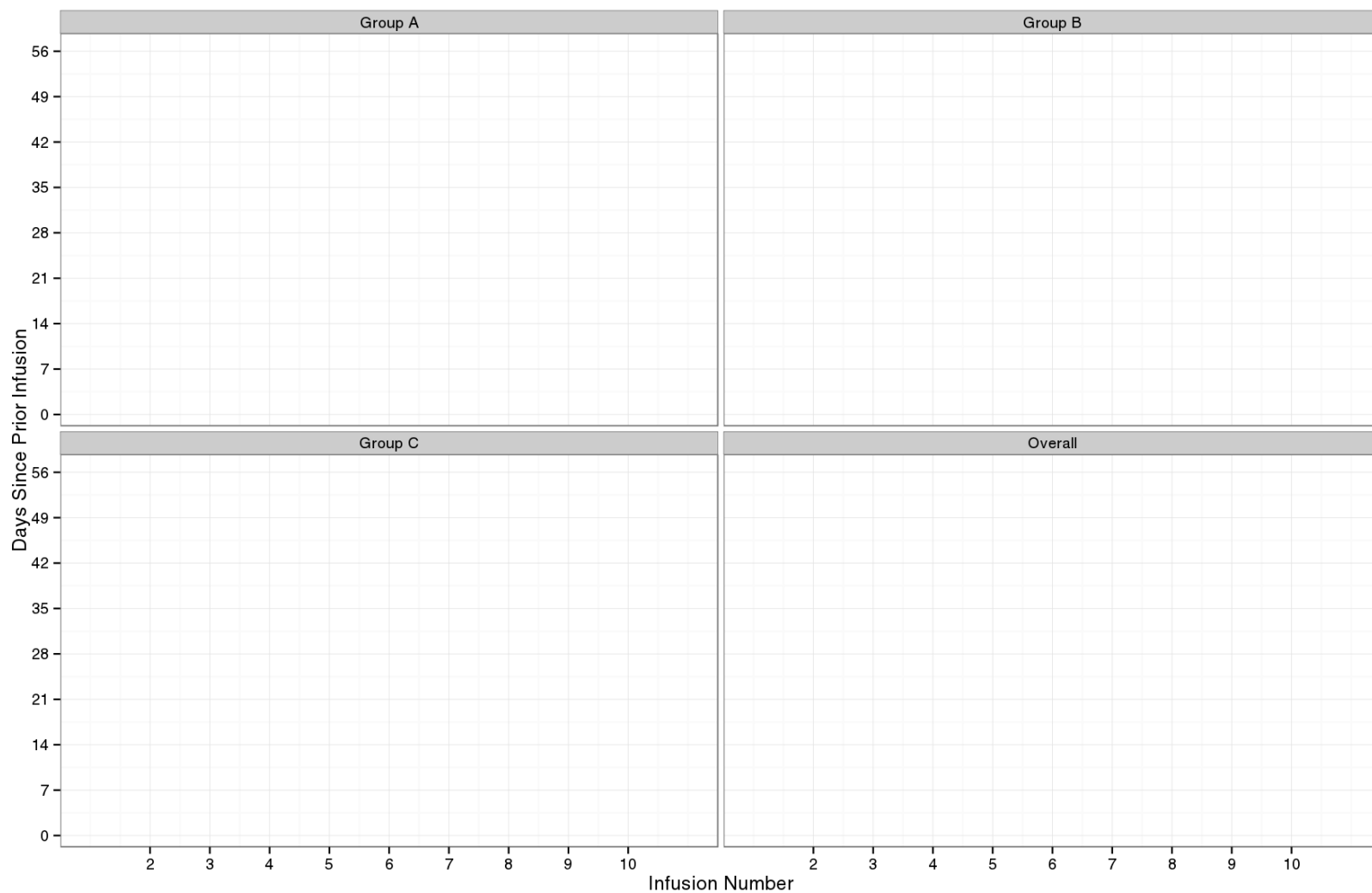
HVTNxxx/HPTNxxx:
 Closed DSMB Report for DSMB meeting on [Date].
 Data Cutoff date:[Date].

Figure 1C. Cumulative Incidence of Discontinued Participation (Dropout or Infusion Discontinuation) by Treatment Assignment



HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 2. Boxplot for Time Between Infusions by Treatment Assignment

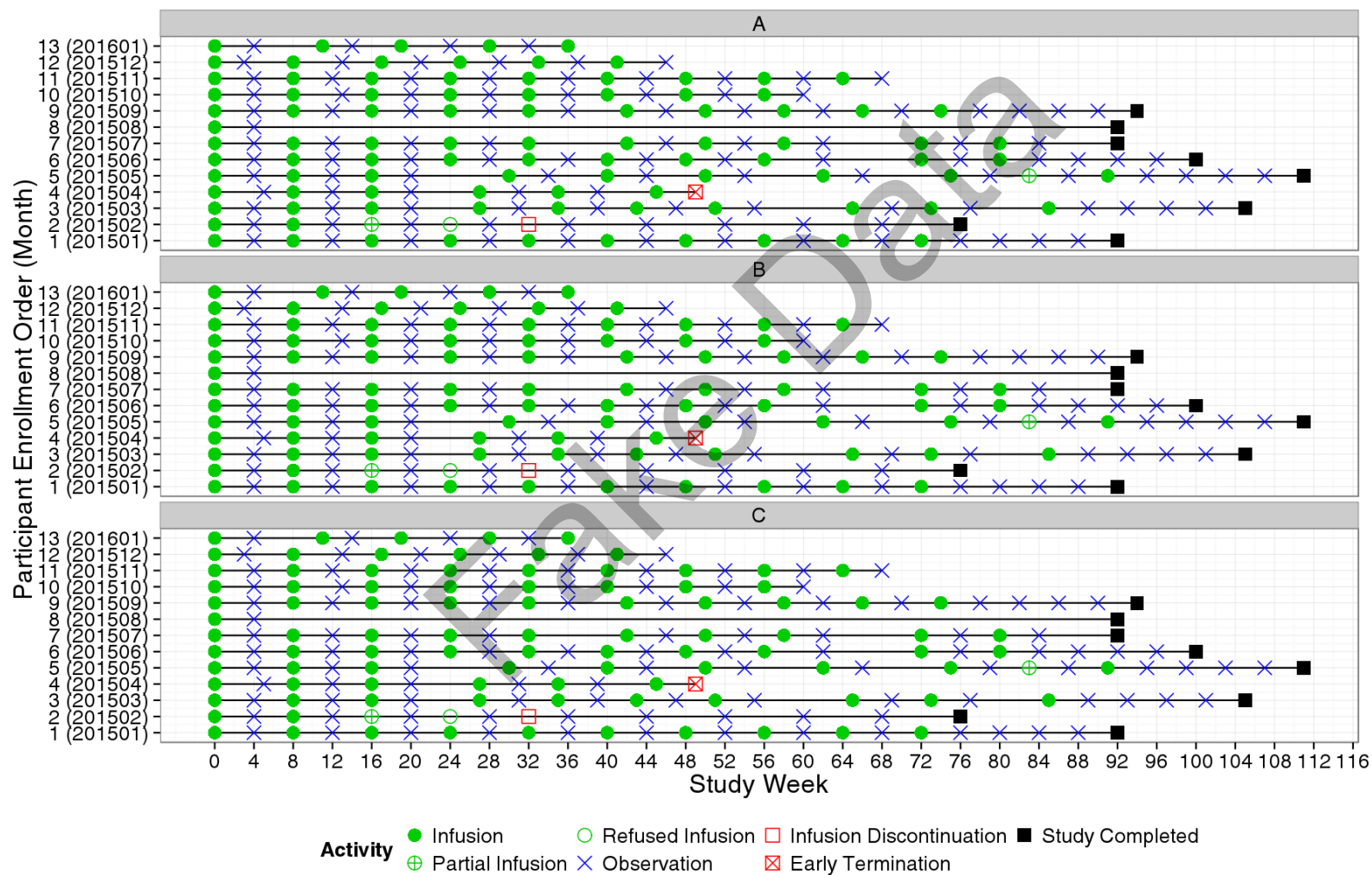


HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 3. Sample of Adherence Patterns over Study Time by Treatment Assignment



HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 7A. Maximum Local Reactogenicity Summary By Treatment Assignment

	Total		A		B		C	
Number Infused	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Tenderness								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain and/or Tenderness								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Erythema								
None or not gradeable	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
6.25 to < 25 cm ² or 2.5 to <5 cm single dim (Gr 1)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
25 to < 100 cm ² or 5 to <10 cm single dim (Gr2)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
>= 100 cm ² or >= 10 cm single dim or severe complication (Gr 3)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
> Potentially life threatening complication (Gr 4)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

NOTE: Events are noted in the category of highest severity grade reported.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 7B. Maximum Systemic Reactogenicity Summary By Treatment Assignment

	Total		A		B		C	
Number Infused	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Malaise and/or Fatigue								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Myalgia								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Headache								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Nausea								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

Events are noted in the category of highest severity grade reported.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 4. Maximum Local Reactogenicity, by Treatment Assignment

Boxplots of local reactogenicity events defined as specific surveyed adverse events that are commonly associated with infusion administration and that have an onset within 3 days following an infusion. Local reactogenicity events assessed in this study are: local pain to the infusion site, local tenderness to the infusion site, erythema at the infusion site, and induration/swelling at the infusion site. Severity definitions are based on The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0 (January 2010).

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 5: Maximum Systemic Reactogenicity, by Treatment Assignment

Boxplots of systemic reactogenicity events defined as specific surveyed adverse events that are commonly associated with infusion administration and that have an onset within 3 days following an infusion. Systemic reactogenicity events are: malaise and/or fatigue, myalgia, headache, nausea, vomiting, chills, arthralgia and body temperature. Severity definitions are based on The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0 (January 2010).

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 8. Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC) by Treatment Assignment, Participant and Decreasing Severity NOTE: * in column 'Non Rept.' indicates non-reportable EAE by DAIDS criteria, as determined by RSC.

Trt.	Publication ID	Severity	EAE Number	Adverse Experience	Onset Date	Relation to Study Product	Medical Officer's Relation to Study Product	Number of Previous Infusions	Days Since Last Infusion	Non Reportable
A	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
B	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
C	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 9. Adverse Events (AEs) by System Organ Class and Severity and Treatment Assignment Sorted by Decreasing Frequency

System Organ Class/ Severity	Total (N=XXXX)		A (N=XXXX)		B (N=XXXX)		C (N=XXXX)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with one or more AEs								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Infections and infestations								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Gastrointestinal disorders								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
General disorders and administration Country conditions								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Respiratory, thoracic and mediastinal disorders								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 10. Grade 3-5 Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment, Sorted by Decreasing Frequency

	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Poisoning and toxicity				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abdominal and gastrointestinal disorders				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Streptococcal Infections				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pain and discomfort NEC				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Viral infections NEC				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100. AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 11. Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment, Sorted by Decreasing Frequency

	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Poisoning and Toxicity				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Streptococcal Infections				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Allergies to foods, food additives, drugs and other chemicals				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 12. Adverse Events (AEs) Related to Study Product by High Level Term and Treatment Assignment

High Level Term/Relationship	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Viral Infections NEC				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Poisoning and Toxicity				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Allergies to foods, food additives, drugs and other chemicals				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mineral and Electrolyte Analyses				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Bronchitis				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Upper respiratory tract infection				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Leukocytoses NEC				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 13A. Distribution of Safety Laboratory Values, by Treatment Assignment

	Total	A	B	C
ALT				
Infusion #1 (baseline)				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Infusion #2				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
....				
Infusion #10				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Hemoglobin				
.				
.				
.				

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 13B. Safety Laboratory Values Meeting Grade 1 AE Criteria or Above, by Treatment Assignment

	Total	A	B	C
ALT				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
...	...	...	...	...
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Hemoglobin				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	...	...	...	...
...	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Platelets				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
...	...	...	...	...
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 6. Boxplot for ALT by Infusion Visit and Treatment Assignment

Figure 7. Boxplot for Hemoglobin by Infusion Visit and Treatment Assignment

Figure 8. Boxplot for Platelets by Infusion Visit and Treatment Assignment

Figure 9. Boxplot for WBC by Infusion Visit and Treatment Assignment

Figure 10. Boxplot for Neutrophil Count by Infusion Visit and Treatment Assignment

Figure 11. Boxplot for Lymphocyte Count by Infusion Visit and Treatment Assignment

Figure 12. Boxplot for Creatinine by Infusion Visit and Treatment Assignment

Graphical presentation of Safety Lab distributions by infusion visit and treatment assignment.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 13. Confirmation/Adjudication Process for HIV Infections

The process of adjudicating HIV infections is outlined in three testing algorithms (Routine, Recent Exposure and Redraw), starting from the time that the initial positive specimen is drawn through the time that the site is notified of a HIV infection.

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 14. Pregnancy Listing

Trt.	Publication ID	LMP Date	Pregnancy outcome date	Date Last Inf. Prior to Outcome	Pregnancy Outcome	Time from Prior Inf. To LMP	# Inf. Prior to LMP	#Inf. Prior to Outcome	Total # Inf.	Comments
A	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
B	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
C	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd-MMM-yyyy	dd-MMM-yyyy	dd-MMM-yyyy	text	text	X	XX	

HVTN_{xxx}/HPTN_{xxx}:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 15. HIV Adjudication Timeline

[illegible]

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

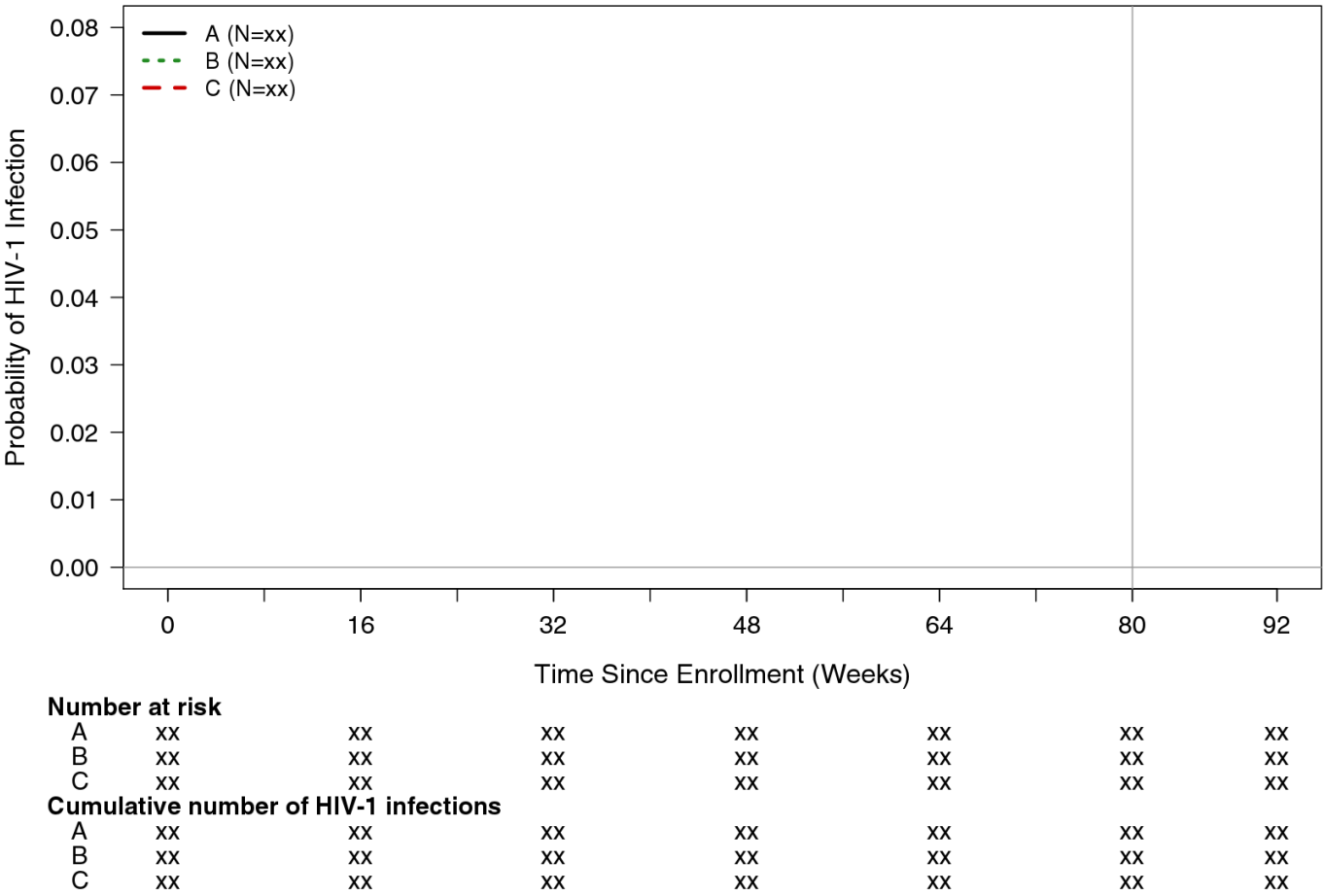
Table 16. HIV Infections

Infection Classification ¹	Trt Group	Publication ID	Initial Positive Sample Draw Date	Initial Positive Sample Draw Visit Number	Initial Positive Sample Draw Study Week	Initial Positive Sample Draw Study Day	Confirmatory Sample Draw	Enrollment Sample RNA Positive	Number of Infusions Received
Pre-Trial	A	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	B	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	C	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
MITT	A	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	B	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	C	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx

¹Infections are categorized as either ‘Pre-Trial’ or ‘MITT’. Infections are ‘Pre-Trial’ if the enrollment sample tested HIV-positive. Pre-Trial infections will be excluded from analysis of the study endpoint as indicated in the protocol.

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 14. Cumulative HIV Incidence Among All MITT Participants by Treatment Arm



HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 17. ART initiation information for HIV infections

Infection Classification ¹	Trt Group	Publication ID	Post-dx ART initiation week	Excluded from primary analysis	Reason for ART initiation
Pre-Trial	A	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	B	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	C	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
MITT	A	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	B	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	C	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text

¹Infections are categorized as either ‘Pre-Trial’ or ‘MITT’. Infections are ‘Pre-Trial’ if the enrollment sample tested HIV-positive. Pre-Trial infections will be excluded from analysis of the study endpoint as indicated in the protocol.

HVTNxxx/HPTNxxx:

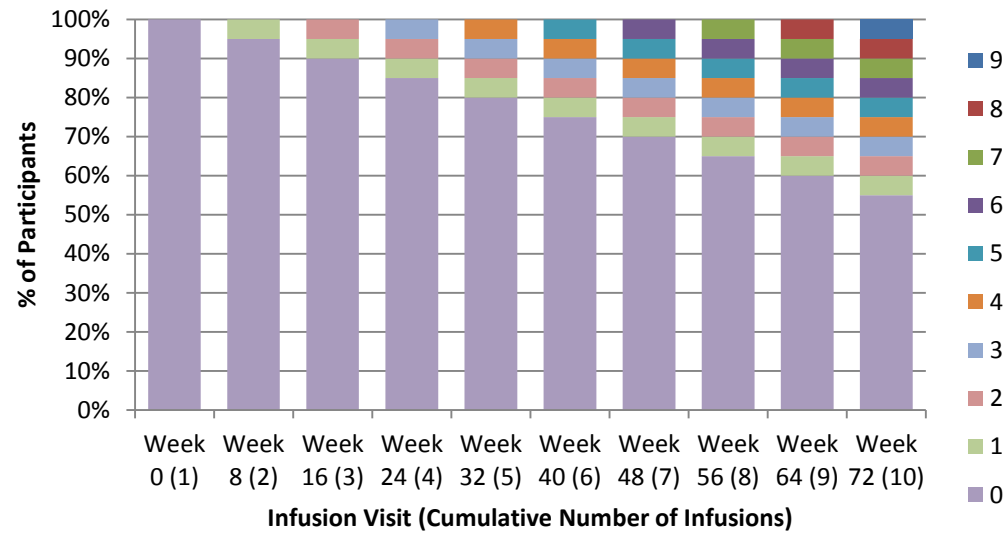
Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 15. Viral Load Over Time Among All Infected MITT Participants

Longitudinal pre-ART viral load measurements are presented by treatment group for MITT infected participants. Individual participant trajectories are indicated by solid black lines, while mean pre-ART viral load measures within a treatment group are plotted using a dashed red line. Means are only estimated for weeks with at least three participants with pre-ART viral load data.

Data Cutoff date:[Date].

[illegible]

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 18a. Visit Retention for All MITT HIV-1 Infected Participants by Treatment Assignment

	Total	A	B	C
Participants Enrolled In Schedule 2	xxx	xxx	xxx	xxx
Week 2 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 4 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)				
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 6 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)				
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				
Week 24 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 18b. Visit Retention for All Pre-Trial HIV-1 Infected Participants and All HIV-2 Infected Participants by Treatment Assignment

	Total	A	B	C
Participants Enrolled In Schedule 3	xxx	xxx	xxx	xxx
Week 2 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 4 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window or did not receive prev. infusion)				
Expected (in visit window and received previous infusion)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 24 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 17. Cumulative Enrollment

Line plot of the observed and expected accrual for all sites combined.

References

- Aalen, O. (1978), “Nonparametric Inference for a Family of Counting Processes,” *The Annals of Statistics*, 6, 701–726.
- Andersen, P., Borgan, O., Gill, R., and Keiding, N. (1993), *Statistical Models Based on Counting Processes*, Berlin and New York: Springer.
- Benkeser, D., Carone, M., and Gilbert, P. B. (2016), “Efficient and robust estimation of cumulative incidence in the presence of competing risks,” *submitted*.
- Breiman, L. (2001), “Random forests,” *Machine learning*, 45, 5–32.
- Breiman, L., Friedman, J. H., Olshen, R. A., and Stone, C. I. (1984), *Classification and regression trees*, Belmont, Calif.: Wadsworth.
- Castillo-Mancilla, J. R., Zheng, J.-H., Rower, J. E., Meditz, A., Gardner, E. M., Predhomme, J., Fernandez, C., Langness, J., Kiser, J. J., Bushman, L. R., and Anderson, P. L. (2013), “Tenofovir, Emtricitabine, and Tenofovir Diphosphate in Dried Blood Spots for Determining Recent and Cumulative Drug Exposure,” *AIDS Research and Human Retroviruses*, 29, 384–390.
- Follmann, D. and Huang, C.-Y. (2015), “Incorporating founder virus information in vaccine field trials,” *Biometrics*, 71, 386–396.
- Freidlin, B., Korn, E. L., and Gray, R. (2010), “A general inefficacy interim monitoring rule for randomized clinical trials,” *Clinical Trials*, 7, 197–208.
- Gilbert, P., Grove, D., Gabriel, E., Huang, Y., Gray, G., Hammer, S., et al. (2011), “A sequential Phase 2b trial design for evaluating vaccine efficacy and immune correlates for multiple HIV vaccine regimens,” *Statistical Communications in Infectious Diseases*, 3.
- Gilbert, P. B., Wei, L. J., Kosorok, M. R., and Clemens, J. D. (2002), “Simultaneous Inferences on the Contrast of Two Hazard Functions with Censored Observations,” *Biometrics*, 58, pp. 773–780.
- Grambsch, P. M. and Therneau, T. M. (1994), “Proportional hazards tests and diagnostics based on weighted residuals,” *Biometrika*, 81, 515–526.
- Grant, R. M., Anderson, P. L., McMahan, V., Liu, A., Amico, K. R., Mehrotra, M., Hosek, S., Mosquera, C., Casapia, M., Montoya, O., Buchbinder, S., Veloso, V. G., Mayer, K., Chariyalertsak, S., Bekker, L.-G., Kallas, E. G., Schechter, M., Guanira, J., Bushman, L., Burns, D. N., Rooney, J. F., Glidden, D. V., and iPrEx study team (2014), “Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study,” *The Lancet. Infectious Diseases*, 14, 820–829.

- Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., Frahm, N., Hural, J., Anude, C., Graham, B. S., Enama, M. E., Adams, E., DeJesus, E., Novak, R. M., Frank, I., Bentley, C., Ramirez, S., Fu, R., Koup, R. A., Mascola, J. R., Nabel, G. J., Montefiori, D. C., Kublin, J., McElrath, M. J., Corey, L., Gilbert, P. B., and Team, H. . S. (2013), “Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine,” *New England Journal of Medicine*, 369, 2083–2092.
- Hernán, M. Á., Brumback, B., and Robins, J. M. (2000), “Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men,” *Epidemiology*, 11, 561–570.
- Heyse, J. F., Kuter, B. J., Dallas, M. J., Heaton, P., and Team, R. S. (2008), “Evaluating the safety of a rotavirus vaccine: the REST of the story,” *Clinical Trials*, 5, 131–139.
- Holm, S. (1979), “A Simple Sequentially Rejective Multiple Test Procedure,” *Scandinavian Journal of Statistics*, 6, 65–70.
- Hubbard, A. E., Kherad-Pajouh, S., and van der Laan, M. J. (2016), “Statistical Inference for Data Adaptive Target Parameters,” *International Journal of Biostatistics*, 12, 3–19.
- Parzen, M., Wei, L., and Ying, Z. (1997), “Simultaneous confidence intervals for the difference of two survival functions,” *Scandinavian Journal of Statistics*, 24, 309–314.
- Rose, S. and van der Laan, M. J. (2011), *Targeted Learning: Causal Inference for Observational and Experimental Data*, Springer Series in Statistics.
- van der Laan, M. J., Polley, E. C., and Hubbard, A. E. (2007), “Super learner.” *Statistical Applications in Genetics and Molecular Biology*, 6, 1–23.

HVTN 704/HPTN 085 and HVTN 703/HPTN 081
Antibody Mediated Prevention Trials Statistical
Analysis Plan for Safety, Trial Monitoring, and
Prevention Efficacy Analysis

October 1, 2020

Michal Juraska, Ph.D.
Allan deCamp, Ph.D.
Deborah J. Donnell, Ph.D.
Peter B. Gilbert, Ph.D.

Fred Hutchinson Cancer Research Center
Vaccine and Infectious Disease Division

Version 3.2

Contents

1	Overview of the Antibody Mediated Prevention Trials	6
2	Objectives and Endpoints of the AMP Trials	6
2.1	Primary Objectives and Endpoints	6
2.2	Secondary Objectives and Endpoints	7
2.3	Exploratory Objectives	7
3	Follow-Up Period	7
4	Study Populations	8
5	Definition of the Primary Efficacy Endpoint (Documented HIV-1 Infection)	9
5.1	HIV Testing Postinfusion	9
5.2	Endpoint Adjudication	10
5.3	Date of the Primary Efficacy Endpoint	10
5.4	Estimated Date of HIV-1 Infection	10
6	Interactions of Study Statisticians with the Data and Safety Monitoring Board	11
7	Statistical Analysis of Safety	12
7.1	Baseline Comparability	12
7.1.1	Reactogenicity	12
7.1.2	AEs and SAEs	12
7.1.2.1	Infusion Reactions	12
7.1.3	Local Laboratory Values	13
7.1.4	Reasons for Infusion Discontinuation and Early Study Termination .	13
8	Statistical Analysis of Prevention Efficacy	13

	3
8.1 Primary Analysis of Prevention Efficacy	14
8.2 Secondary Analyses of Prevention Efficacy	17
8.2.1 Analyses of Prevention Efficacy for HIV-1 Infections After the Week 80 Visit	21
8.3 Prevention Efficacy Against Measured Neutralization Sensitive Viruses . . .	21
8.3.1 Final Analyses Also Included in Interim Analyses	21
8.3.2 Additional Analyses Included in the Final Analysis	22
8.3.3 Prevention Efficacy Accounting for Number of Founding Viruses . . .	22
8.4 Analysis of Exploratory Objective 1	22
8.5 Analysis of Exploratory Objective 2	22
8.6 Analysis of Exploratory Objective 3	23
9 Trial Monitoring	28
9.1 Feasibility Check and Guideline for Continuing Enrollment as Planned . . .	28
9.2 Sequential Monitoring of Prevention Efficacy for Potential Harm, Non-Efficacy, and High Efficacy	30
9.2.1 Potential harm monitoring	32
9.2.2 Non-efficacy monitoring	33
9.2.2.1 Unblinded conditional power assessment at an interim analysis	34
9.2.2.2 Estimated prevention efficacy by measured VRC01 neutral- ization sensitivity	34
9.2.3 High efficacy monitoring	34
9.2.4 Rationale for starting non-efficacy/high efficacy monitoring at at least 45 total infections	35
9.3 Monitoring of the Use of PrEP	35
9.3.1 Simulation Study for PrEP Monitoring	38
9.4 Monitoring for Futility to Assess Prevention Efficacy	40
9.4.1 Estimation of the number of HIV-1 infection endpoints at an interim analysis	42
9.4.2 A Bayesian model for the HIV-1 incidence rate in estimation of the number of HIV-1 infection endpoints at an interim analysis	45

	4
9.4.2.1 Estimation of the total person-years at risk (T^*)	46
9.5 Monitoring for Performance Standards of Quality of Trial Conduct	46
9.5.1 Expanded details for reporting on item 4: quality and timeliness of HIV-1 diagnostic testing	47
9.5.2 Expanded details for reporting on item 5: quality and timeliness of data collected on case report forms	47
10 Statistical Software	48
11 Roles of Study Statisticians	48
Appendix A	48
Appendix B	90
Appendix C	175
References	196

List of Tables

1	Operational rules for right-censoring of times-to-event at the Week 80 visit	15
2	Super Learner library for estimation of cumulative incidence of the primary efficacy endpoint in the pooled mAb and the control arms	19
3	Summary of sequential monitoring of PE for each AMP trial	31
4	Potential harm monitoring stopping boundaries for each AMP trial	33
5	Estimated rates of PrEP use and estimated percent person-years on effective PrEP use	37

1 Overview of the Antibody Mediated Prevention Trials

The Antibody Mediated Protection (AMP) trials consist of two harmonized protocols, HVTN 704/HPTN 085 and HVTN 703/HPTN 081, which evaluate the safety and efficacy of VRC01, a broadly neutralizing monoclonal antibody (mAb) against the CD4 binding site of the HIV-1 envelope glycoprotein administered in 10 IV infusions every 8 weeks, in reducing acquisition of HIV-1 infection. HVTN 704/HPTN 085 enrolls 2700 HIV-uninfected men and transgender persons (TG) in North and South America (U.S., Switzerland, Peru, Brazil) who have anal sex with men or TG, and HVTN 703/HPTN 081 enrolls 1900 HIV-uninfected sexually active women in sub-Saharan Africa (South Africa, Botswana, Malawi, Kenya, Zimbabwe, Mozambique, and Tanzania). Study participants are randomized to receive a 10 mg/kg or a 30 mg/kg dose of VRC01 or a control preparation. Participants are tested for HIV-1 infection every 4 weeks and at any time following participant report of possible HIV-1 exposure during the study. Enrollment in both AMP trials is completed by the earliest event of reaching full enrollment or September 30, 2018.

2 Objectives and Endpoints of the AMP Trials

HVTN 704/HPTN 085 and HVTN 703/HPTN 081 are two randomized, double-blind, placebo-controlled Phase 2b test-of-concept HIV prevention trials, conducted in HIV-uninfected adults at risk for HIV infection.

2.1 Primary Objectives and Endpoints

Primary objective 1:

To evaluate the safety and tolerability of VRC01 mAb administered through IV infusion

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, AEs, SAEs, and rates of discontinuation

Primary objective 2:

To determine if the VRC01 mAb prevents HIV-1 infection and to estimate the level of efficacy

Primary endpoint 2:

Documented HIV-1 infection by the Week 80 study visit

2.2 Secondary Objectives and Endpoints

Planned statistical analyses for secondary objective 1 is described in the separate Correlates of Prevention Efficacy Statistical Analysis Plan.

Secondary objective 1:

To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Secondary endpoints 1:

Serum concentration of VRC01 in participants assigned to receive the mAb (ELISA, neutralizing assay)

Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint

Sequences of breakthrough HIV infections from the earliest available HIV-positive plasma samples

VRC01 neutralization-sensitivity of, and effector function against, HIV strains from infected trial participants from the earliest available postHIV-infection serum samples

2.3 Exploratory Objectives

Exploratory objective 1:

To assess use of FTC/TDF in the study cohort

Exploratory objective 2:

To assess if prevention efficacy is modified by FTC/TDF use

Exploratory objective 3:

To understand changes in risk behavior and the potential for risk compensation for all study participants

Exploratory objective 4:

To measure anti-idiotypic antibodies to VRC01

3 Follow-Up Period

All participants will be followed for 104 weeks (i.e., 2 years) post-enrollment. Week 80 is the last study visit for the primary efficacy endpoint analysis. To allow retrospective testing of any infection diagnoses detected up until Week 88 as primary endpoints by Week 80, the final efficacy analysis will be triggered when the last enrolled participant reaches the Week 88 visit. Week 104 is the last study visit for the co-primary endpoint analysis of safety and

tolerability. Participants who are diagnosed with HIV-1 infection during the study will be followed for approximately 6 months following infection diagnosis.

4 Study Populations

We define three study cohorts that are analyzed for addressing various study objectives. This terminology is used throughout this SAP.

- **Safety Cohort:** all randomized participants who receive the first infusion
- **Modified Intent-to-Treat (MITT) Cohort:** participants in the Safety Cohort who are not later discovered to have been HIV-infected on the date of the first infusion (Day 0) and who are not involved in a duplicate enrollment
- **Per-Protocol (PP) Cohort:** MITT participants who receive all planned infusions within the target infusion-visit windows

The Safety Cohort and the MITT Cohort are very similar but not identical to a full Intention-to-Treat Cohort (i.e., all randomized participants); the Safety Cohort differs by excluding randomized volunteers who do not enroll; and the MITT Cohort is a subset of the Safety Cohort that also excludes randomized participants discovered later to have been HIV-positive by Day 0. Due to blinding and the brief length of time between randomization and enrollment (typically no more than 4 working days), we expect almost all randomized participants to be in the Safety Cohort. Given that eligibility for the study requires recent evidence of being HIV-1 uninfected (within 30 days prior to enrollment), we expect almost all enrolled participants to be in the MITT Cohort.

The PP Cohort membership status is defined at each fixed study time point for a participant, with inclusion defined by receiving all planned infusions within the target infusion-visit windows up to that point of time or up to the time of HIV-1 infection diagnosis, whichever occurs earlier. This time-dependent cohort definition is necessary given that participants experiencing the HIV infection primary endpoint are not given infusions post HIV infection diagnosis. Consequently, the analyses for assessing prevention efficacy in the MITT and PP cohorts handle time differently—the former compare infection rates between treatment groups in the fixed MITT cohort defined at baseline whereas the latter compare infection rates between treatment groups whose membership changes over time based on infusion adherence data. In particular, at a given study time a participant is in the PP cohort if they have received all planned infusions within the target infusion-visit windows up to that point of time or up to the time of HIV-1 infection diagnosis, whichever occurs earlier.

All analyses of safety objectives are based on the Safety Cohort. All analyses of prevention efficacy are based on the MITT cohort unless explicitly demarcated otherwise. Analyses of

correlates of prevention efficacy are based on participants in cohorts defined in the Correlates of Prevention Efficacy SAP.

Prevention efficacy analyses will be based on data from MITT participants treated according to the initial randomization assignment regardless of how many infusions they received (i.e., treated “as randomized”). Additionally, secondary efficacy analyses will be performed in the PP Cohort, which will be analyzed on the “as-treated” basis (actually received treatments).

In the unexpected event of a duplicate enrollment, the interim safety and infusion discontinuation data will be reported for each enrollment, considering these as separate participants, while noting in the report that a duplicate enrollment occurred. The final safety report will include only the safety and infusion discontinuation data following the first randomization, analyzed according to the randomized treatment assignment. The immunogenicity and prevention efficacy analyses will exclude all data from participants with a duplicate enrollment regardless of whether also duplicate randomization occurred or not.

5 Definition of the Primary Efficacy Endpoint (Documented HIV-1 Infection)

5.1 HIV Testing Postinfusion

The prevention efficacy endpoint is diagnosis of HIV-1 infection during the follow-up period. Following enrollment, HIV testing will take place at scheduled clinic visits.

HIV testing is performed using the protocol-specific HIV testing algorithms (see Study-Specific Procedures). At scheduled visits that include HIV testing, specimens will be tested with an FDA-approved 4th generation HIV-1/2 enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA). If the participant has a reactive test result, an HIV RNA test and an HIV-1/2 discriminatory test will be performed as indicated in the algorithm. Further HIV testing is required using a second specimen drawn on a later date to confirm a diagnosis of HIV infection. The second specimen may be collected at an interim visit. Samples to be stored for future studies will also be collected at this time.

A ‘case’ is defined as a participant who is confirmed to have acquired HIV-1 infection after enrollment based on the protocol-specific diagnostic algorithms (see SSP). Before informing a participant that they are infected at or after enrollment, all HIV test results will be reviewed by a blinded, independent Endpoint Adjudicator(s) or designee(s). Only HIV-1 infection cases confirmed by the Endpoint Adjudicator(s) will be counted as HIV-1 infections in the analysis.

5.2 Endpoint Adjudication

The general diagnostic criteria for HIV infection are well accepted. However, definitive diagnosis of HIV infection in the context of having received a study product that is even partially effective may be more difficult. Specifically, if VRC01 is capable of completely suppressing viral replication, or if the antibody alters the normal serological response upon exposure to HIV, standard diagnostic tests may be more difficult to assess. Therefore, the Endpoint Adjudicator(s) will review all serological and virological test results in a blinded manner for each participant who tests positive per the trials' diagnostic testing algorithms. The Endpoint Adjudicator(s) will also review HIV test results in cases where HIV infection status is not clearly resolved using the HIV testing algorithm. The assessment of the Endpoint Adjudicator(s) or designee(s) will be reported to the SDMC and to the HIV diagnostics laboratory.

The Endpoint Adjudicator(s) or designee(s) must notify the SDMC within 1 working day of any confirmed HIV infection. The HIV diagnostics lab will inform the clinic of the outcome of the HIV testing algorithm (i.e., HIV-infected, HIV-uninfected, or redraw required).

The Endpoint Adjudicator(s) or designee(s) will be expert in the fields of infectious diseases or laboratory medicine independent of the Vaccine Research Center and clinical investigators participating in this trial. A separate Standard Operating Procedure will govern the activities of the Endpoint Adjudicator(s) or designee(s).

5.3 Date of the Primary Efficacy Endpoint

The Endpoint Adjudicator(s) will define the date of diagnosis based on his/her judgment of all of the available diagnostic data. This date is assigned based only on diagnostic results collected prospectively over time; it does not consider the results of HIV-specific PCR tests that may be performed on earlier samples that are tested later. The date of HIV-1 infection diagnosis will be used as the event-date for primary time-to-event analyses of Primary Endpoint 2 (documented HIV-1 infection) and for all secondary time-to-event analyses of Primary Endpoint 2 that analyze time since enrollment as the failure time variable.

5.4 Estimated Date of HIV-1 Infection

For all participants diagnosed with HIV-1 infection, the sample available at the nearest date before the diagnosis date will be tested using HIV-specific PCR. If it is positive, then the sample at the second nearest date before the diagnosis date will be tested using HIV-specific PCR. This 'look-back' procedure will be repeated until an HIV-specific PCR negative test result is obtained or until a test is done for a Day 0 sample. The complete HIV diagnostic test history including retrospective testing is used to estimate the date of infection as described in detail in Section 4.2 of the Correlates of Prevention Efficacy SAP. The estimated infection

date will be used as the event-date for secondary analyses of Primary Endpoint 2 that analyze time since last infusion received prior to the estimated infection date as well as for marker correlates and sieve analyses of breakthrough HIV-1 infections (see the Correlates of Prevention Efficacy SAP for details) and may also be used for exploratory analyses of the primary efficacy endpoint. The estimator for the date of HIV-1 infection may be refined to be based on additional data beyond the diagnostic testing information (details of this estimator are described in the Correlates of Prevention Efficacy SAP).

6 Interactions of Study Statisticians with the Data and Safety Monitoring Board

At each 6-monthly Data and Safety Monitoring Board (DSMB) meeting, the study statisticians will present Open and Closed Reports separately for each AMP trial; all tables and figures included in the Closed Report are specified in Appendix A with statistical analyses of safety further described in Section 7. For a subset of tables and figures in the Closed report, the Open Report includes tables and figures with the same information except with trial information presented pooled across the three treatment groups to preserve blinding to treatment assignment. In addition, the following trial monitoring reports will be presented at each DSMB meeting, separately for each AMP trial:

- feasibility monitoring report per Section 9.1 starting after approximately and not fewer than 120 enrolled participants have expected follow-up through to the end of the Week 32 visit;
- monitoring report of prevention efficacy for potential harm, non-efficacy, and high efficacy per Section 9.2, where
 - potential harm monitoring is commenced at the 20th pooled primary efficacy endpoint and is continually performed with each additional endpoint until the time non-efficacy/high efficacy monitoring is triggered,
 - non-efficacy monitoring is commenced at at least 45 but no more than 67 pooled primary efficacy endpoints, and
 - high efficacy monitoring is commenced at the same time as non-efficacy monitoring;
- monitoring report for the use of Truvada as pre-exposure prophylaxis per Section 9.3;
- monitoring report for futility to assess prevention efficacy per Section 9.4 starting after at least 12 months after the first participant is enrolled; and
- monitoring report for performance standards of quality of trial conduct per Section 9.5.

7 Statistical Analysis of Safety

Since enrollment is concurrent with receiving the first infusion, all enrolled participants will have received at least 1 infusion and therefore will provide some safety data.

7.1 Baseline Comparability

Treatment groups will be compared for baseline characteristics including demographics and laboratory measurements, using descriptive statistics (percentages, means, ranges).

7.1.1 Reactogenicity

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participants reactogenicity will be counted once under the maximum severity for all infusion visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration, or erythema, and of systemic symptoms will be calculated. Kruskal-Wallis tests will be used to test for differences in severity between arms.

7.1.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show by treatment arm the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product. A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last infusion, and number of infusions received.

7.1.2.1 Infusion Reactions

A descriptive analysis of infusion reactions is provided for DSMB review at the 6-monthly meetings. The analysis includes the assessment of cumulative incidence of *the first occurrence* of (i) any infusion reaction, and (ii) each of the four clinical categories (also referred to as types) of an infusion reaction (urticarial reaction, dyspnea with rash, dyspnea without rash, and other reaction) as a function of the number of received infusions. For both (i) and (ii), time to an infusion reaction is measured in terms of the number of infusions received by the onset time.

We estimate the first occurrence of (i) using the complement of the Kaplan-Meier estimator for the survival function and pointwise 95% Wald confidence intervals (CIs). Participants who did not experience an infusion reaction contribute partial (i.e., right-censored) information in the analysis. In addition, sample proportions of received infusions that led to a first infusion reaction as a function of the infusion number are reported with 95% exact binomial CIs.

We estimate the first occurrence of (ii) using the Aalen-Johansen estimator for the type-specific cumulative incidence function within the competing risks survival analysis framework.

Note that an estimated cumulative incidence function, overall or type-specific, can only be reliably interpreted at timepoints with sufficiently large numbers at risk to ensure stability of the estimators.

7.1.3 Local Laboratory Values

Box plots of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the DAIDS AE Grading Table will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

7.1.4 Reasons for Infusion Discontinuation and Early Study Termination

The number and percentage of participants who permanently discontinue infusions and who terminate the study early will be tabulated by reason and treatment arm.

8 Statistical Analysis of Prevention Efficacy

Except where specified, all prevention efficacy endpoint analyses are performed in the MITT cohort. All analyses only use samples and data collected prior to study unblinding. Unless either of the trials is stopped prematurely, the common data cut date for the final prevention

efficacy analysis in both trials is set to be April 3, 2020.

All analyses specified in Sections 8.1, 8.2, and 8.3 are conducted in each AMP trial separately, as well as pooled over the two AMP trials. The statistical methods are the same, except the pooled analyses additionally stratify for study. For cumulative incidence-based pooled analyses, stratification is performed by estimating the cumulative hazard separately within each combination of study and treatment group (requiring at least 10 total primary HIV-1 infection endpoints within each combination of study and treatment group), and, for Cox model-based pooled analyses, stratification is performed by using a separate baseline hazard for each study (requiring at least 10 total primary HIV-1 infection endpoints within each study to include the trial as a stratification covariate).

8.1 Primary Analysis of Prevention Efficacy

The time between enrollment and the date of HIV-1 infection diagnosis determined according to Section 5.3 is evaluated in the MITT cohort. The failure times of participants never observed to be diagnosed with HIV-1 infection are right-censored at the date of the last HIV-negative test or the Week 80 visit, whichever occurs earlier.

Let PE denote the overall prevention efficacy by the Week 80 visit of the 10 mg/kg and 30 mg/kg mAb groups pooled together compared to the control group. We define the primary PE parameter as

$$PE = \left\{ 1 - \text{cumulative incidence ratio (pooled mAb groups/control group)} \right. \\ \left. \text{of the primary efficacy endpoint by the Week 80 visit} \right\} \times 100\%, \quad (1)$$

where the cumulative incidence ratio is the probability of the primary efficacy endpoint by the Week 80 visit for participants assigned to receive the mAb divided by the probability of the primary efficacy endpoint by the Week 80 visit for participants assigned to receive control. More specifically, the primary PE parameter, $PE(t)$, will be estimated at a fixed time point t chosen to be the latest possible time point when stable estimation using follow-up data through the Week 80 visit can be achieved; this is operationalized by defining t as the maximum time point with 150 participants at risk for the primary endpoint in each of the placebo and individual VRC01 groups. All times-to-event will be right-censored at the Week 80 visit or earlier following the operational rules summarized in Table 1. Note that the fixed time point t will likely differ for the two AMP trials given the dynamic visit windows. By definition of the stratified estimator, the trial-pooled analysis will use the smaller of the two fixed time points t . Additionally, note that, due to differences between Schedules 1 and 4, the operational rules in Table 1 imply that an infection endpoint observed in Schedule 4 after the hypothetical Schedule 4 Week 80 visit would be excluded from primary endpoints, while an infection endpoint observed in Schedule 1 at the same time post-enrollment would be included as a primary endpoint if the endpoint was registered before or at the Schedule 1 Week 80 visit.

Table 1: Operational rules for right-censoring of times-to-event at the Week 80 visit

HIV status	Visit attendance scenario		Censoring rule
HIV-Uninfected	Attended s1 wk 80 visit		Censor at s1 wk 80 sample draw date
	Missed s1 wk 80 visit	Attended s1 post-wk 80 visit	Censor at target s1 wk 80 visit date
		Attended s4 post-wk 80 visit	Censor at maximum of (hypothetical s4 wk 80 visit ¹ , last s1 sample draw date)
		Did not attend post-week 80 visit in s1 or s4	Censor at last HIV-uninfected sample draw date
HIV-Infected	Infected in s1 on or before s1 wk 80 visit		Infected, use adjudicated diagnosis date
	Infected in s1 after s1 wk 80 visit	Attended s1 wk 80 visit	Censor at s1 wk 80 sample draw date
		Evidence of HIV-negative status at post-s1 wk 80 visit	Censor at target s1 wk 80 visit date
		No evidence of HIV-negative status at post-s1 wk 80 visit	Censor at last HIV-uninfected sample draw date
	Entered s4 at or before hypothetical s4 wk 80 visit ¹	Infected on or before hypothetical s4 wk 80 visit	Infected, use adjudicated diagnosis date
		Evidence of HIV-negative status at post-hypothetical s4 wk 80 visit	Censor at hypothetical s4 wk 80 visit ¹ date
		No evidence of HIV-negative status at post-hypothetical s4 wk 80 visit	Censor at last HIV-uninfected sample draw date
	Entered s4 after the hypothetical s4 wk 80 visit and diagnosed after the first s4 visit		Censor at maximum of (hypothetical s4 wk 80 visit, last s1 HIV-uninfected sample draw date)
	Entered s4 after the hypothetical s4 wk 80 visit and diagnosed immediately		Censor at last s1 HIV-uninfected sample draw date ²

- Abbreviations: wk = visit label for target visit week as defined in the study protocol (Appendix J for Schedule 1 and Appendix M for Schedule 4), s1 = Schedule 1, s4 = Schedule 4.
- Actual visit dates may differ from the implied week in the target visit label due to (1) dynamic visit scheduling in schedule 1, and (2) visit windows in schedules 1 and 4.
- All censoring times are based on sample draw dates or target visit dates (where appropriate). Visit windows are not used because (1) Schedule 1 and Schedule 4 visit windows are quite different (s1 allowable wk 80 visit window is +/- 7 days, s4 allowable windows are -41/+42 days), and (2) since a hypothetical wk 80 visit is constructed in s4, unnecessarily complicated to construct a hypothetical s4 wk 80 visit window, which would overlap with other s4 visit windows if the same pattern were followed and would be an entirely unique visit window if no overlap were ensured.
- ¹Hypothetical s4 week 80 visit is defined as exactly 560 days post-enrollment. Justification: unlike s1, s4 visits are all relative to enrollment and occur independently of each other, so it's preferable to define a hypothetical wk 80 visit as 560 days post-enrollment than to use a midpoint estimator and/or some other dynamic method which doesn't correspond to s4's structure.
- ²If a participant enters s4 at wk 88 or wk 104 and is immediately diagnosed, cannot determine whether infection occurred in s1 (clearly before the target s1 wk 80 visit) or in s4 (clearly after the hypothetical s4 wk 80 visit).

Each of the two cumulative incidence parameters in (1) will be estimated using the transformed Nelson-Aalen estimator for the cumulative hazard function evaluated at time t defined in the preceding paragraph. We will use the delta method to obtain the asymptotic 95% CI for the log cumulative incidence ratio (pooled mAb/control) and then back-transform these confidence bounds to the PE scale. Both the point estimate and the 95% CI for PE will be reported. If there are more than 10 HIV-1 primary endpoints in each of the VRC01 dose groups, then the Nelson-Aalen estimator for the cumulative hazard function will be computed separately for each dose group and the weighted average of the dose group-specific estimates, with the weight 0.5 assigned to each dose group, will be transformed for inference about PE. The variance estimate of the overall averaged cumulative hazard estimator will be used to obtain the variance estimate on the log cumulative incidence ratio scale for calculating confidence intervals. For trial-pooled analyses, if there are more than 10 primary endpoints in each stratum defined by trial and treatment group, the Nelson-Aalen estimator

will be computed separately in each of the 6 strata (4 VRC01 dose group strata and 2 control group strata), and separate weighted averages of the VRC01 dose-group and control-group stratum-specific estimates, with weights 0.25 assigned to each VRC01 dose-group stratum and weights 0.5 assigned to each control-group stratum, will be transformed for inference about the trial-pooled PE.

PE is the target parameter for the primary analysis of overall PE. The primary analysis tests the null hypothesis

$$H_0 : PE = 0\% \text{ versus the alternative hypothesis } H_1 : PE \neq 0\% \quad (2)$$

using a 2-sided $\alpha = 0.05$ level Wald test of the equality of log cumulative hazard functions at 80 weeks for the pooled mAb group and the control group. Note that the critical value for determining whether the effect of VRC01 on prevention of HIV-1 acquisition is significant at the two-sided 0.05 level will not require adjustment for the interim monitoring of PE for potential harm, non-efficacy, and high efficacy described in Section 9.2. This is because this monitoring is designed to have minimal impact on the type-I error/power of the study. Moreover, whereas interim monitoring for positive PE would mean that the actual type-I error of the study is inflated above the nominal level, interim monitoring for potential harm, non-efficacy, and high efficacy has the effect of decreasing the actual type-I error rate below the nominal level. In other words, use of the unadjusted critical value leads to conservative (as opposed to anti-conservative) inference, and our simulations show that the degree of conservatism is minimal.

The timing of infections will be described separately for the pooled mAb group and the control group by the respective cumulative incidence curves of the time between first infusion and the date of HIV-1 infection diagnosis. Each curve will be estimated by a transformed Nelson-Aalen estimator for the cumulative hazard function. To obtain a pointwise 95% CI, we will use the delta method to obtain the asymptotic 95% CI for the log cumulative incidence over time and then exponentiate the confidence bounds. As for PE, if there are more than 10 HIV infection events in each of the VRC01 dose groups, then the above estimators will be computed separately for each dose group and aggregated for inference on the pooled mAb group cumulative incidence.

Additionally, cumulative PE over time will be reported. To obtain pointwise 95% CIs, first we will use the delta method to obtain asymptotic 95% CIs for the log cumulative incidence ratio (pooled VRC01/control) over time and then back-transform the confidence bounds to the PE scale. The simultaneous 95% confidence interval for cumulative PE over time will be obtained following the method of Parzen, Wei, and Ying (1997). The same method will be applied to obtain an estimate of cumulative PE on the additive difference-scale (control group minus pooled VRC01 group) with pointwise and simultaneous 95% confidence intervals. This analysis is informative because it communicates about benefits and risk on an absolute scale: for example under the assumption that assignment to a VRC01 arm does not increase the risk of infection for any participant, the estimate at a given time t is interpreted as the probability a participant assigned to a VRC01 arm has their infection averted compared to, counter to fact, had they been assigned to placebo.

8.2 Secondary Analyses of Prevention Efficacy

Secondary analyses assess PE parameters for the mAb dose groups separately. Let PE10 be the overall prevention efficacy of the 10 mg/kg mAb group and let PE30 be the overall prevention efficacy of the 30 mg/kg mAb group, defined as

$$PE10 = \left\{ 1 - \text{cumulative incidence ratio (mAb 10 mg/kg group/control group)} \right. \\ \left. \text{of the primary efficacy endpoint by 80 weeks} \right\} \times 100\%,$$

and

$$PE30 = \left\{ 1 - \text{cumulative incidence ratio (mAb 30 mg/kg group/control group)} \right. \\ \left. \text{of the primary efficacy endpoint by 80 weeks} \right\} \times 100\%.$$

The PE10 and PE30 parameters will be assessed using the same estimation method as described in Section 8.1.

We will conduct secondary analyses to test the null hypotheses

$$H_0 : PE10 = 0\% \text{ versus the alternative hypothesis } H_1 : PE10 \neq 0\%$$

and

$$H_0 : PE30 = 0\% \text{ versus the alternative hypothesis } H_1 : PE30 \neq 0\%$$

using 2-sided $\alpha = 0.05$ level Wald tests described in Section 8.1. Both unadjusted p-values and Holm–Bonferroni-adjusted p-values (Holm, 1979) will be reported for each of the individual dose versus control group analyses.

In addition, the following secondary analyses of PE will be conducted:

- (i) Assess a dose-response effect by testing the null hypothesis
 H_0 : cumulative HIV-1 incidence by 80 weeks is equal in the three study groups versus
 H_1 : $0\% \leq PE10 \leq PE30$ with at least one strict inequality.
- (ii) Test the null hypothesis that the cumulative HIV-1 incidence by 80 weeks is equal in the three study groups versus the alternative hypothesis that there are some differences.
- (iii) Test the null hypothesis that the cumulative HIV-1 incidence by 80 weeks is equal in the two mAb groups versus the alternative hypothesis that PE30 is greater than PE10, which would demonstrate that assignment to a higher mAb dose level causes higher PE.

Hypotheses (i)–(iii) will be tested using cumulative hazard function based Wald tests. Define the Wald test statistic

$$W_{i,j} = \frac{\log \hat{\Lambda}_i(80 \text{ weeks}) - \log \hat{\Lambda}_j(80 \text{ weeks})}{\sqrt{\widehat{\text{var}}\{\log \hat{\Lambda}_i(80 \text{ weeks})\} + \widehat{\text{var}}\{\log \hat{\Lambda}_j(80 \text{ weeks})\}}},$$

where $\hat{\Lambda}(\cdot)$ is the Nelson-Aalen estimator and $i, j \in \{c, 10, 30\}$, $i \neq j$, represent the control, 10 mg/kg mAb, and 30 mg/kg mAb group, respectively. The test statistic considers the estimated variance of the Nelson-Aalen estimator proposed in Aalen (1978).

The alternative hypothesis in (i) is equivalent to $\tilde{H}_1 : \Lambda_c(t_0) \geq \Lambda_{10}(t_0) \geq \Lambda_{30}(t_0)$, $t_0 = 80$ weeks, with at least one strict inequality, and therefore the test of (i) will reject H_0 if both $W_{c,10} \geq \Phi^{-1}(0.975)$ and $W_{10,30} \geq \Phi^{-1}(0.975)$, where Φ^{-1} is the quantile function of the standard normal distribution. The test of (ii) will reject H_0 if at least one of $|W_{c,10}| \geq \Phi^{-1}(0.975)$ and $|W_{10,30}| \geq \Phi^{-1}(0.975)$ holds. The test of (iii) will reject H_0 if $W_{10,30} \geq \Phi^{-1}(0.975)$.

As a supportive analysis of the hypotheses in (2), targeted minimum loss-based estimation (TMLE) may be used to estimate cumulative incidences of the primary efficacy endpoint over time for the pooled mAb arm and the control arm. Iterative mean-based TMLE is used for this analysis as described in Benkeser, Carone, and Gilbert (2016). The Super Learner (van der Laan, Polley, and Hubbard, 2007) is used to generate initial estimates of the conditional censoring distribution and the iterated conditional means. The Super Learner library includes both parametric and nonparametric algorithms: generalized linear models, generalized additive models with 2 or 3 degrees of freedom, a regression tree (Breiman et al., 1984), and a random forest (Breiman, 2001) (specified in Table 2). Each method considers adjustment for baseline demographic covariates, the baseline behavioral risk score built via supervised learning as described in Section 8.6, and two-way interactions of these terms. The baseline demographics to adjust for are country (if there are at least 10 total primary HIV-1 infection endpoints in a country – otherwise categories are collapsed) and AMP study (for analyses that pool the two AMP trials). The candidate algorithms in the Super Learner library consider various adjustments for time, as shown in Table 2. TMLE analyses will produce plots of estimated cumulative PE on both the multiplicative mAb efficacy and additive-difference scales, as done for the primary analyses. The TMLE analyses will be implemented using the *survtmle* R package available at CRAN.

PE parameters will be estimated by 1 minus the ratio (pooled mAb groups/control group) of these tMLE estimators. Influence-curve based variance estimators of each cumulative incidence is used, and the delta method applied to obtain the variance estimator of the log cumulative incidence ratio. Point estimates and 95% pointwise and simultaneous Wald CIs for cumulative incidence curves and $PE(t)$ curves will be plotted. For the final timepoint of 80 weeks, 2-sided Wald p-values will be reported.

In addition to studying PE based on cumulative incidences of the primary efficacy endpoint over time, secondary analyses will assess hazard ratio based PE defined as

$$PE = \left\{ 1 - \text{hazard ratio (pooled mAb groups/control group)} \right. \\ \left. \text{of the primary efficacy endpoint at 80 weeks} \right\} \times 100\%. \quad (3)$$

The PE parameter in (3) will be estimated using a Cox proportional hazards model with the indicator of assignment to a mAb group versus the control group as the sole covariate. The

Table 2: Models included in the Super Learner library. Z denotes a mAb group assignment, B baseline behavioral risk score as described in Section 8.6, and W a vector of baseline demographic covariates. The columns indicate what type of model was used (glm = generalized linear model, step = stepwise glm using both AIC and BIC as selection criteria, and gam = generalized additive model), how time was modeled ($\emptyset$ denotes time was omitted from the model, **factor(t)** indicates dummy variables were used), and what covariates were included ($x * y$ indicates a cross product between covariates x and y). We use $s(x; df = d)$ to denote that variable x was modeled using a polynomial spline of degree d .

Model type	Time	Covariates
Conditional mean estimates		
glm	$\emptyset$	Z
glm	$\emptyset$	$Z + B + W$
glm	$\emptyset$	$Z * B$
step	$\emptyset$	$Z * B + W$
Censoring estimates		
glm	factor(t)	$\emptyset$
glm	factor(t)	$Z * t$
glm	$\emptyset$	Z
glm	$\emptyset$	$Z + B + W$
glm	t	Z
glm	t	$Z + B + W$
glm	$\log(t)$	Z
glm	$\log(t)$	$Z + B + W$
step	factor(t)	$Z + B + W$
step	t	$Z + B + W$
step	$\log(t)$	$Z + B + W$
gam	$s(t, 3)$	Z
gam	$s(t, 3)$	$Z + B + W$
gam	$s(t, 2)$	Z
gam	$s(t, 2)$	$Z + B + W$

score test will be used to evaluate whether hazard ratio PE differs from zero. This analysis uses the same failure time as used for the primary analysis of the cumulative-incidence based PE. Goodness-of-fit diagnostics including the complementary log-log endpoint-free survival curves and the Grambsch and Therneau (1994) test will be applied to assess veracity of the proportional hazards assumption.

This Cox model analysis will be repeated, conducted as an as-treated analysis of the per-protocol (PP) cohort. This analysis is done using the same Cox model except that participants are right-censored by the event of no longer qualifying for membership in the PP

cohort.

An additional secondary analysis of PE based on the Cox proportional hazards model will be done that uses as the failure time variable the time from the most recent infusion to the estimated date of HIV-1 infection. This analysis is conducted in the MITT cohort. This analysis can have increased power to detect prevention efficacy compared to the primary analysis of the cumulative incidence based parameter PE, if instantaneous prevention efficacy is higher when VRC01 concentrations are higher. Goodness-of-fit diagnostics will be applied as described above.

The Cox models are selected for the secondary analysis instead of the primary analysis in order that the validity and interpretation of the primary analysis does not depend on the proportional hazards assumption.

The Cox model may also be used for a secondary analysis to assess PE in the MITT cohort by modeling full cumulative infusion adherence (i.e., at study time t , all infusions up to and including time t received within target visit windows) or lack thereof as a binary time-varying covariate. In addition, to study the dose-response in the association of infusion adherence with PE, we will assess PE in subgroups defined by the level of cumulative infusion adherence over time, with adherence levels defined, at time t , as missing zero infusions by time t , missing at most 1 infusion by time t , missing at most 2 infusions by time t , etc., included in the model as binary time-varying covariates. If there is a time-varying covariate prognostic for subsequent HIV-1 infection that also predicts the probability of subsequently taking infusions, and taking infusions predicts subsequent values of this prognostic factor, then the Cox model described above provides biased inference (Hernán et al., 2000). Based on this, diagnostics will be done to check if there are any measured time-varying covariates strongly associated with both infection and taking subsequent infusions. If such covariates are identified, then the standard Cox model analysis described above will be supplemented with a causal structural nested Cox model analysis, which is designed to correct for time-varying confounding.

Sensitivity analyses of the primary analysis will test $H_0 : PE = 0\%$ with a log-rank test and with a Gehan-Wilcoxon test stratified by VRC01 dose group.

To further explore potential time-variations in PE from Week 0 through to Week 80, instantaneous PE over time, defined as one minus the instantaneous hazard ratio (pooled VRC01/control) over time, will be estimated using the nonparametric kernel estimation method with optimal bandwidth selection for the instantaneous hazard ratio as described in Andersen et al. (1993), with an asymptotic pointwise 95% CI. The simultaneous 95% confidence interval for instantaneous PE will be calculated following the method of Gilbert et al. (2002).

8.2.1 Analyses of Prevention Efficacy for HIV-1 Infections After the Week 80 Visit

The primary analyses of prevention efficacy and the Cox model secondary analyses of prevention efficacy will be repeated including all MITT HIV-1 infections in the analysis occurring through to the Week 104 terminal study visit. These analyses are relevant because the right-tail of VRC01 concentration may be long enough that protection against infection could occur even against HIV-1 infections many weeks or months after the last VRC01 infusion.

8.3 Prevention Efficacy Against Measured Neutralization Sensitive Viruses

8.3.1 Final Analyses Also Included in Interim Analyses

For each primary HIV-1 infection endpoint, neutralization sensitivity of the majority breakthrough founding virus (and of other founding minor viral variants with frequency greater than 10%) at the first HIV-1 RNA positive time point to the VRC01 clinical lot is measured by three independent replicates of IC50 and IC80 from the TZM-bl target cell assay. (A ‘founder virus’ is an HIV-1 variant that is measured/observed based on sequencing the earliest available post-infection sample.) For each geometric mean readout (across the three replicates) of IC50 and IC80 separately, majority founder viruses are divided into five categories of sensitivity level (“sensitivity type”): Sensitive = $< 0.3 \mu\text{g/mL}$; Moderately Sensitive = $0.3\text{--}1 \mu\text{g/mL}$; Intermediate = $1\text{--}3 \mu\text{g/mL}$; Moderately Resistant = $3\text{--}10 \mu\text{g/mL}$; and Resistant = $> 10 \mu\text{g/mL}$. For infected cases with multiple assayed HIV-1 variants, the geometric mean IC50 and IC80 pertaining to the most sensitive variant is used for analysis. The report will include a table of the distributions of the number of HIV-1 infected cases (and/or assayed variants) by treatment assignment and sensitivity type, and boxplots of the distributions of geometric mean IC50 and IC80 readouts for infected cases by treatment assignment.

In addition, for each sensitivity type category, for IC50 and IC80 separately, the following results are presented:

- Estimated cumulative incidence curves of each HIV-1 sensitivity type by treatment assignment (Aalen-Johansen estimator)
- Estimated cumulative prevention efficacy curve for each HIV-1 sensitivity type (contrast of Aalen-Johansen estimates)
- Estimated proportional hazards prevention efficacy by quantitative $\log_{10}$ IC50 or $\log_{10}$ IC80 (method of Juraska and Gilbert (2013))

If the number of primary endpoint counts in some sensitivity type categories is small, then adjacent categories may be combined, to ensure at least 5 endpoints total per analyzed category.

8.3.2 Additional Analyses Included in the Final Analysis

All of the primary and secondary analyses of overall prevention efficacy specified in Sections 8.1 and 8.2 will be repeated for the endpoint HIV-1 infection with sensitivity type Sensitive or Moderately Sensitive according to the definitions above. The statistical methods are the same, except cumulative incidence estimators are replaced with cause-specific cumulative incidence estimators and Cox model analyses right-censor primary HIV-1 infection endpoints of a different sensitivity type.

8.3.3 Prevention Efficacy Accounting for Number of Founding Viruses

Another secondary analysis may be conducted to assess the effect of VRC01 on prevention of HIV-1 acquisition over 80 weeks using the method of Follmann and Huang (2015) that incorporates information on the number of HIV-1 founder viruses in HIV-1-infected participants. The method has increased efficiency relative to Cox proportional hazards regression if VRC01 reduces the number of founders.

8.4 Analysis of Exploratory Objective 1

The use of oral FTC/TDF as PrEP will be assessed as described in Section 9.3.

8.5 Analysis of Exploratory Objective 2

If there is substantial PrEP use detection at baseline, then the Cox model will be used to assess whether prevention efficacy significantly differs in subgroups with detectable versus undetectable baseline PrEP use, and to make inferences on prevention efficacy separately in each subgroup. In addition, if there is substantial PrEP use detected over the course of the study, then a marginal structural Cox model will be used to assess prevention efficacy in the sub-population not using PrEP.

More specifically, the primary analysis will be repeated where only MITT infection endpoints with no evidence of PrEP use at the time of HIV-1 diagnosis and at the time of the earliest evidence of infection will be included in the analysis. Intracellular TFV concentration (see Section 8.4) will be used to determine eligibility for this analysis. A participant is eligible if the TFV concentration is below the lower limit of detection as defined above at the diagnosis visit and at the visit with earliest evidence of HIV-1 infection (if different from

the diagnosis visit). Since the ARVs are only detectable in plasma for roughly 14 days (Patterson et al. 2010) and some participants may have become infected before the 14-day window, with this approach we are not assured that all those included in the analysis were not using prophylactic ARVs at the time of infection. Therefore an additional analysis may be conducted that addresses this issue by also excluding participants from the HIV-1 acquisition analysis if they self-reported ARV use in the last 30 days at either the diagnosis visit or the last visit prior to diagnosis. These analyses will evaluate uninfected participants without accounting for data on their TFV concentrations.

8.6 Analysis of Exploratory Objective 3

Several analyses will make use of components of a 2-dimensional predicted HIV-1 risk score, which refers to identified best models predicting the conditional probability that a participant who is HIV-1-negative at $t_0 = 0$ weeks becomes HIV-1-positive by a fixed time point $t_1 = 80$ weeks (and $t_1 = 104$ weeks) given a set of baseline input variables W and treatment stratum $Z \in \{\text{control, pooled VRC01}\}$.

The first step in the prediction problem involves, for each $Z = z$ separately, estimating

$$\psi_{0,z}(W) = P_0(T \leq 80 \text{ weeks} \mid T > 0 \text{ weeks}, W, Z = z),$$

where T is a time from enrollment to the primary endpoint event (the parameter of interest for $t_1 = 104$ weeks is defined analogously). It has been shown that this parameter is identifiable based on observed data in a trial with a time-to-event endpoint. The procedure for estimating $\psi_{0,z}(W)$ is fully described in the “Statistical Analysis Plan for HIV-1 Risk Prediction in KwaZulu-Natal via Superlearner” developed by Alex Luedtke and Ernesto Ulloa (downloadable from <https://www.overleaf.com/read/bkycmxsdzzvm>), with all modifications described in the following paragraphs.

All estimators will be trained and applied separately in each AMP trial given major differences in demographics, risk behavior, and viral transmission and epidemiology between the two trial populations. Moreover, in the control-group risk prediction in HVTN 703/HPTN 081, two data sets will be used for training all estimators: Initially, we will restrict the training set to primary follow-up in HVTN 703/HPTN 081 control recipients only. Subsequently, we will enrich this training set by including 80 weeks of blinded follow-up in the HVTN 702 trial’s combined control and vaccine female recipients who were enrolled at overlapping sites with HVTN 703/HPTN 081. We will refer to these as the restricted and enriched control groups, respectively, in HVTN 703/HPTN 081.

In each AMP trial, the estimation will be carried out separately in the control (restricted and enriched for HVTN 703/HPTN 081) and pooled VRC01 groups, i.e., the estimators will be trained separately on data from participants in the control and pooled VRC01 groups (estimation in individual VRC01 dose groups is not considered due to potential convergence failures and limited precision). The best-performing estimator $\hat{\psi}_z$ for $\psi_{0,z}$ will also

be identified independently for each $z \in \{\text{control, pooled VRC01}\}$ in each trial. For the control-group prediction in HVTN 703/HPTN 081, the candidate estimators including the superlearner trained on the restricted control-group data and the candidate estimators including the superlearner trained on the enriched control-group data will be all evaluated together for prediction accuracy, identifying a single best-performing estimator across both the restricted and enriched control-group data sets. For the i -th enrolled participant with a baseline covariate vector W_i , the predicted HIV-1 risk score is then defined as the ordered pair $\left(\hat{\psi}_{\text{control}}(W_i), \hat{\psi}_{\text{pooledVRC01}}(W_i)\right)$ of the best-performing estimators.

In more detail, within each combination of trial and treatment stratum, a set of candidate estimators $\{\hat{\psi}_1, \dots, \hat{\psi}_K\}$, specified in Table 5 in the KwaZulu-Natal risk prediction SAP, and a superlearner estimator $\hat{\psi}_{SL}$ for $\psi_{0,z}$ will first be constructed following Algorithm 1 below. The best-performing estimator $\hat{\psi}_z$ is defined as an estimator from the set $\{\hat{\psi}_1, \dots, \hat{\psi}_K, \hat{\psi}_{SL}\}$ with maximal cross-validated AUC in the treatment stratum $Z = z$ (see Algorithm 2 below). Following identification of the best-performing estimator in each treatment stratum, we will compute the estimated/predicted HIV-1 risk score for all enrolled participants.

The covariate vector W will consist of participant-level baseline demographic characteristics and baseline behavioral survey responses. The baseline demographic characteristics include clinical site, country of residence, race, ethnicity, and age in both trials, and, in addition, gender identity in HVTN 704/HPTN 085. The behavioral risk survey consists of 88 questions that aim to assess the risk of HIV infection and can be previewed in Appendix B. HVTN 703/HPTN 081 participants enrolled at clinical sites outside of South Africa were administered an abbreviated form of the behavioral survey consisting of a subset of 60 questions (Appendix C). In order to maximize the use of covariate information, missing responses in the full set of survey questions selected for inclusion in W (a subset of the 88 questions) will be imputed using the missForest method (Stekhoven and Bühlmann, 2011), implemented in the `missForest` R function, for participants outside of South Africa using observed responses from participants enrolled in South Africa. The missForest method uses random forests to multiply impute mixed-type data. This method does not require tuning parameters or distributional assumptions and has been shown to perform comparably to or better than other commonly used multiple imputation methods such as multivariate imputation by chained equations or k -nearest neighbors. Since this analysis considers a large fraction of imputed responses for some behavioral risk variables, another set of superlearner estimators will be fit using only the abbreviated survey, and the best-fitting model will be identified from the pooled set of estimators based on the full/imputed and the abbreviated behavioral risk covariate vectors in this trial.

The risk score computation involves the following steps: Initially, baseline variables with a large portion of missing responses or sparse response levels will be excluded upfront from the input covariate data set, and for a given $\hat{\psi}_z(W)$, only a subset of the 88 behavioral survey variables and the aforementioned demographic variables will be included in W . Then, the missForest method will be used to multiply impute missing covariate values in W . Next, to accommodate a high-dimensional W , dimension-reducing screening methods will be used

for “classical” algorithms. Modified versions of screening methods in **SuperLearner**’s R functions `screen.glmnet` and `screen.randomforest` for the time-to-event outcome will be used as two screening algorithms combined with each prediction algorithm. More specifically, a Cox model with lasso penalty will be used in `screen.glmnet`, and a survival forest (R function `rsfc`) will be used in `screen.randomforest`. In `screen.randomforest`, the top 20 variables with the greatest variable importance index will be screened in. Lastly, the estimators will be trained using the screened-in covariates, the prediction accuracy will be evaluated, and the best-performing estimators will be used for predicting HIV-1 risk in each treatment stratum.

For the HVTN 703/HPTN 081 enriched control-group candidate estimators, W will consist of the baseline demographic characteristics specified above and the questionnaire data from the HVTN 702 behavioral risk assessment. The HVTN 702 behavioral risk assessment consists of 23 questions which, like the HVTN 703/HPTN 081 behavioral risk survey, aim to assess risk of HIV infection. Some questions in the HVTN 702 assessment correspond, in part, to questions in the full HVTN 703/HPTN 081 survey but are structured differently. Questions between the two assessments which capture similar information (e.g., number of sex partners) will be consolidated into a single feature where possible. Survey items in the HVTN 702 survey that were not included in the full HVTN 703/HPTN 081 survey (e.g., age at sexual debut) will be multiply imputed using the `missForest` method. No other covariates from the full HVTN 703/HPTN 081 survey will be used in fitting the enriched control-group candidate estimators. Note that imputation of the enriched data set will be performed separately from the imputation of the restricted HVTN 703/HPTN 081 survey described above. Since this analysis considers a large fraction of imputed responses, another set of candidate estimators will be fit using only the questions that are shared between the HVTN 702 and the full HVTN 703/HPTN 081 surveys. The best-fitting estimator will be identified from the pooled set of estimators based on the complete/imputed and the restricted/enriched control-group data sets in HVTN 703/HPTN 081.

Internal validation of $\hat{\psi}_z(W)$ (see Algorithm 2 below) will be based on cross-validated predictions using only data from the AMP trials (with no additional external training set to train the learners). External validation will not be performed. Computation time of `survtmle` scales with the resolution of T . To limit computation time, person-time will be rounded up to the nearest month.

Pseudocode for Superlearner and Candidate Estimators

Let A_z denote observed data from participants in treatment stratum z in a single AMP trial.

Algorithm 1 Superlearner and candidate estimators

Input: A_z and $\hat{\psi}_1, \dots, \hat{\psi}_K$ prediction algorithms

- 1: Use A_z to impute A_z^* via package `missForest`
 - 2: Use package `survtmle` on A_z^* to obtain $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}$, $\forall i \in A_z^*$ [†]
 - 3: Partition A_z^* into 10 folds, with $A_{z,1}^*, \dots, A_{z,10}^*$ denoting validation sets
 - 4: **for** $j = 1, \dots, 10$ **do**
 - 5: **for** $k = 1, \dots, K$ **do**
 - 6: Fit $\hat{\psi}_{k,j}$ on training set $A_{z,-j}^*$ pertaining to $A_{z,j}^*$ [‡]
 - 7: Let $j(i) = j$ for all $i \in A_{z,j}^*$
 - 8: **end for**
 - 9: **end for**
 - 10: Using $\{\hat{\psi}_{k,j(i)}(W_i), \hat{D}_i^{(1)}, \hat{D}_i^{(2)} : i \in A_z^*, k \in \{1, \dots, K\}\}$, obtain optimal $\alpha = (\alpha_1, \dots, \alpha_K)$ using package `nloptr`
 - 11: Repeat steps 3–10 five times to obtain $\alpha^* = \frac{1}{5} \sum_{r=1}^5 \alpha^{(r)}$
 - 12: **for** $k = 1, \dots, K$ **do**
 - 13: Fit algorithm $\hat{\psi}_k$ on A_z^* [‡]
 - 14: **end for**
 - 15: Let $\hat{\psi}_{SL}(w) = \sum_{k=1}^K \alpha_k^* \hat{\psi}_k(w)$
- Output:** $\hat{\psi}_k(W_i)$, $k = 1, \dots, K$, and $\hat{\psi}_{SL}(W_i)$ for all $i \in A_z^*$
-

[†] Following Section 3 in the KwaZulu-Natal risk prediction SAP, `survtmle` is run twice to obtain the individual i -specific quantities $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}$, defined as the sum of the point estimate of the marginal survival probability $P(T \in (t_0, t_1])$ and $P(T > t_1)$, respectively, plus the corresponding individual i -specific efficient influence function estimate output by `survtmle`. $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}$ are then used to estimate the cross-validated risk, which is minimized with respect to the superlearner weights.

[‡] Some data adaptive algorithms such as `glmnet` may require another layer of cross-validation.

Pseudocode for Internal Validation Algorithm

Let A_z denote observed data from participants in treatment stratum z in a single AMP trial.

Algorithm 2 Internal Cross-validation

Input: A_z and $\hat{\psi}_1, \dots, \hat{\psi}_K$ prediction algorithms

- 1: Partition A_z^* into 10 folds, with $A_{z,1}^*, \dots, A_{z,10}^*$ denoting validation sets
- 2: **for** $s = 1, \dots, 10$ **do**
- 3: Use training set $A_{z,-s}$ to impute $A_{z,-s}^*$ via package **missForest**
- 4: Use package **survtmle** on $A_{z,-s}^*$ to obtain $\hat{D}_{s,i}^{(1)}$ and $\hat{D}_{s,i}^{(2)}, \forall i \in A_{z,-s}^*$ [†]
- 5: Partition $A_{z,-s}^*$ into 10 folds, with $A_{z,-s,1}^*, \dots, A_{z,-s,10}^*$ denoting validation sets
- 6: **for** $j = 1, \dots, 10$ **do**
- 7: **for** $k = 1, \dots, K$ **do**
- 8: Fit $\hat{\psi}_{k,j}$ on training set $A_{z,-s,-j}^*$ pertaining to $A_{z,-s,j}^*$ [‡]
- 9: Let $j(i) = j$ for all $i \in A_{z,-s,j}^*$
- 10: **end for**
- 11: **end for**
- 12: Using $\{\hat{\psi}_{k,j(i)}(W_i), \hat{D}_{s,i}^{(1)}, \hat{D}_{s,i}^{(2)} : i \in A_{z,-s}^*, k \in \{1, \dots, K\}\}$, obtain optimal $\alpha = (\alpha_1, \dots, \alpha_K)$ using package **nloptr**
- 13: Repeat steps 5–12 five times to obtain $\alpha_s^* = \frac{1}{5} \sum_{r=1}^5 \alpha^{(r)}$
- 14: **for** $k = 1, \dots, K$ **do**
- 15: Fit algorithm $\hat{\psi}_k$ on $A_{z,-s}^*$ [‡]
- 16: **end for**
- 17: Let $\hat{\psi}_{SL,s}(w) = \sum_{k=1}^K \alpha_{s,k}^* \hat{\psi}_k(w)$
- 18: Let $s(i) = s$ for all $i \in A_{z,s}$
- 19: **end for**
- 20: Use A_z to impute A_z^* via package **missForest**
- 21: Use package **survtmle** on A_z^* to obtain $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}, \forall i \in A_z^*$ [†]
- 22: Compute $\widehat{AUC}_{CV}$ for each $\hat{\psi}_k$ and $\hat{\psi}_{SL}$ using $\{\hat{\psi}_{k,s(i)}(W_i), \hat{\psi}_{SL,s(i)}(W_i), \hat{D}_i^{(1)}, \hat{D}_i^{(2)} : i \in A_z^*\}$

Output: $\widehat{AUC}_{CV}$ for $\hat{\psi}_k, k = 1, \dots, K$, and $\hat{\psi}_{SL}$ for A_z^*

[†] Following Section 3 in the KwaZulu-Natal risk prediction SAP, **survtmle** is run twice to obtain the individual i -specific quantities $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}$, defined as the sum of the point estimate of the marginal survival probability $P(T \in (t_0, t_1])$ and $P(T > t_1)$, respectively, plus the corresponding individual i -specific efficient influence function estimate output by **survtmle**. $\hat{D}_i^{(1)}$ and $\hat{D}_i^{(2)}$ are then used to estimate the cross-validated risk, which is minimized with respect to the superlearner weights.

[‡] Some data adaptive algorithms such as **glmnet** may require another layer of cross-validation.

9 Trial Monitoring

The AMP trials are monitored in four ways: (1) feasibility monitoring for retention and adherence to infusions; (2) sequential monitoring of prevention efficacy; (3) monitoring for futility to assess prevention efficacy, defined as an inability to answer the primary efficacy objective in a timely manner; and (4) operational monitoring for other performance standards of quality of trial conduct. Data on these monitoring activities are collated into interim reports and are presented to the independent DSMB every 6 months. While guidelines for trial modifications based on the monitoring operate separately for the two AMP trials, the same multinational DSMB monitors the two trials, facilitating its ability to account for all information when making recommendations. Following each DSMB meeting, the DSMB reports to the Oversight Committee (OC) a summary of the trial review, which may include recommendations to modify or terminate the trial for one or both study cohorts. The following descriptions apply to each trial separately.

9.1 Feasibility Check and Guideline for Continuing Enrollment as Planned

A feasibility monitoring report is developed as soon as approximately and not fewer than 120 enrolled participants have expected follow-up through to the end of the Week 32 visit window. This feasibility monitoring is based on the first four 8-week infusion intervals (Weeks 1 through 32) and evaluates whether an adequately high percentage of participants attend clinical visits and receive the infusions per the protocol.

The guideline is based on an adequately high rate of study participation (participants remain engaged in the trial and have not declined further infusions) supplemented by data on visit attendance, which corresponds to adherence to receipt of infusions.

As stated in the protocol, the following guideline is used for continuing enrollment as planned:

- Continued participation by the Week 32 visit pooled over the three treatment groups is greater than 80%.

If this treatment group-blinded criterion fails to be met, the Protocol Team, in discussions with the DSMB and OC, will discuss whether modification or termination of the trial is warranted.

Here we expand upon the details of the feasibility guideline and on the output included in the feasibility check monitoring report.

Discontinued participation is assessed using multiple event definitions indicating discontinued participation, in order to capture different reasons for discontinuation that have different

impacts on the ability of the trials to meet their primary efficacy objectives. In particular, the following five definitions (with their purposes summarized) will be analyzed:

1. CRF-confirmed permanent discontinuation of study product administration prior to study completion, with discontinuation due to a safety issue or refusal to continue taking infusions. [*Addresses if infusions are too onerous*]
2. The same as Definition 1 except only including discontinuation due to a safety issue [*Addresses if infusions are too onerous due to a safety issue*]
3. The same as Definition 1 except only including discontinuation due to refusal to continue undergoing infusions. [*Addresses if infusions are considered too onerous due to a non-safety reason*]
4. Permanent discontinuation of study product administration for any reason other than a safety issue or refusal to continue taking infusions. This definition includes CRF-confirmed study termination due to lost contact with participant or 20 consecutive weeks without any participant contact. [*Addresses discontinued infusions or loss to follow-up for reasons other than safety or refusal, with no information available on whether the loss was related to infusions being onerous*]
5. The first event of Definitions 1 and 4 [*Addresses discontinued infusions for any reason including loss to follow-up*]

Definition 1 aims to measure discontinued participation due to the infusion process being too onerous, which could occur either because of a safety issue or because of refusal to continue receive infusions. Definitions 2 and 3 measure discontinued participation due to the two component events comprising Definition 1 (safety and refusal, respectively), thereby isolating two reasons for discontinued infusions. These types of discontinued participation are the most serious in that a high rate would indicate an infeasibility of the VRC01 intervention, and therefore Definitions 1, 2, 3 are the most important for measuring feasibility of the intervention. As such the 80% feasibility guideline is interpreted primarily for Definition 1.

Definition 4 measures discontinued participation due to reasons other than safety or refusal including loss to follow-up, which is based on either CRF-confirmed loss or an operational definition of a loss to follow-up event not captured on a CRF. Given that loss to follow-up is expected to frequently occur for reasons different from the infusion process being too onerous (i.e., for reasons that would occur in efficacy trials of other HIV prevention interventions, such as moving), this type of discontinued participation is less serious, where the study could still be made feasible under moderate rates of loss to follow-up, by enrolling additional study participants.

Definition 5 counts as discontinued participation any reason for discontinuation or loss to follow-up, whichever occurs first. Thus this definition measures permanent ceasing of infusions without distinguishing the reason.

For each definition of discontinued participation, the analysis counts discontinued participation events. First, we define discontinued participation as a record on a CRF confirming permanent discontinuation of study product administration prior to study completion, with discontinued participation by Week 32 defined as this date occurring before or on the Week 32 visit date, or, if the visit was not yet attended, before or on the date defining the end of the Week 32 visit window. For Definition 5, the Kaplan-Meier estimator will be used to estimate and display the probability of discontinued participation over time, starting at study entry through to the time period during which data are available (which will extend at least through the Week 32 visit window). For all other definitions, a competing risks failure time analysis is used that studies the time until the first event of a type specified in a given definition. For these competing risks analyses a participants follow-up is right-censored by the occurrence of another discontinuation event type that is not included in the definition under consideration. For these competing risks analyses each time-to-event curve is estimated using the Aalen-Johansen estimator, which in particular yields an estimate of the probability of discontinuation due to the event type by the Week 32 visit. For Definition 1 right-censoring is by loss to follow-up (using the operational Definition 4); for Definition 2 right-censoring is by loss to follow-up (using the operational Definition 4) and by discontinuation due to refusal; for Definition 3 right-censoring is by loss to follow-up (using the operational Definition 4) and by discontinuation due to a safety issue; and for Definition 4 right-censoring is by discontinuation due to Definition 1 (a safety issue or refusal).

Appendix A includes mock tables on expected versus observed visit attendance (Table 5A) and on infusion adherence (Table 5B) patterns that will be reported at the 6-monthly DSMB meetings. All of this output will be included in the feasibility check monitoring report, focusing on the first five infusion visits (Week 0, 8, 16, 24, 32).

9.2 Sequential Monitoring of Prevention Efficacy for Potential Harm, Non-Efficacy, and High Efficacy

For each trial, PE is monitored by the independent DSMB at each DSMB meeting, with triggers based on numbers of primary HIV-1 infection endpoints for when the DSMB meetings begin to include formal evaluation of the potential harm, non-efficacy, and high efficacy stopping boundaries (these triggers are described below). The approach to sequential monitoring of PE is similar to that described in Gilbert, Grove et al. (2011). The monitoring of PE in the AMP trials is also similar to that used for the HVTN 505 phase 2b HIV-1 vaccine efficacy trial (Hammer et al., 2013). Each of the AMP trials uses sequential monitoring of the pooled mAb groups versus control to stop early for:

- potential harm [establish that PE (pooled over the mAb groups) $< 0\%$ based on a 2-sided monitoring-adjusted 90% confidence interval lying below 0%]
- non-efficacy [establish that PE (pooled over the mAb groups) $< 40\%$ based on a 2-sided 95% nominal confidence interval lying below 40%]

Table 3: Summary of sequential monitoring of PE for each AMP trial

Monitoring Type	Hypotheses	Testing Approach	Size/Power	Monitoring Plan	Number of Interim Analyses
Potential Harm	$H_0 : PE \geq 0\%$ vs. $H_1 : PE < 0\%$	Exact 1-sided binomial test of the proportion of infections assigned to a mAb group	1-sided $\alpha = 0.05$	Near-constant* 1-sided p-value cut-off controlling the FWER at $\alpha = 0.05$	After every infection from 20 th total until first non-efficacy analysis
Non-Efficacy	$H_0 : PE \geq 40\%$ vs. $H_1 : PE < 40\%$	Wald test	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI supplemented with conditional power	6-monthly starting after at least 45 but no more than 67 total infections [†]
High Efficacy	$H_0 : PE \leq 70\%$ vs. $H_1 : PE > 70\%$	Wald test	1-sided $\alpha = 0.025$	Nominal 2-sided 95% CI	6-monthly starting at the same time as for non-efficacy

*An increasing per-test alpha until a constant level is reached that, if applied to all subsequent tests, maintains the specified FWER

[†]The first non-efficacy/high efficacy interim analysis occurs either at the scheduled DSMB meeting at which there are 45 or more primary endpoint events across the three study groups or when 67 total primary endpoint events are observed, whichever occurs earlier.

- high efficacy [establish that PE (pooled over the mAb groups) $> 70\%$ based on a 2-sided 95% nominal confidence interval lying above 70%].

The sequential monitoring for non-efficacy and high-efficacy is based on 2-sided 95% confidence intervals in order that the result of the study that would be reported in the abstract of a journal article would convey convincing evidence supporting the conclusion of non-efficacy or high efficacy. Freidlin, Korn, and Gray (2010) discuss a rationale for this approach to non-efficacy monitoring. The sequential monitoring for potential harm is based on 2-sided 90% confidence intervals for prudence to protect the safety of study participants, i.e., less precision is required to meet a guideline for potential harm than to meet guidelines about non-efficacy or high efficacy. The sequential monitoring plan for each AMP trial is summarized in Table 3.

The potential harm monitoring is done after every primary endpoint event starting at the 20th total pooled over the three treatment groups, through to the time at which the non-efficacy/high efficacy monitoring commences. Once the non-efficacy/high efficacy monitoring begins, the non-efficacy monitoring serves the purpose of detecting a harmful effect of the mAb to elevate the endpoint rate compared to control. The details of the procedures used for the three monitoring guidelines are described next. In addition to these monitoring guidelines that are based on parameters aggregating all primary HIV-1 infection events over follow-up,

the statistical reports including non-efficacy/high efficacy monitoring will also graphically report estimates of cumulative HIV-1 incidence over time by study arm and estimates of cumulative prevention efficacy over time for high dose vs. placebo and for low dose vs. placebo.

9.2.1 Potential harm monitoring

Heyse et al. (2008) and the HVTN 505 phase 2b HIV-1 vaccine efficacy trial (Hammer et al., 2013) are examples of randomized, placebo-controlled efficacy trials that used continuous monitoring for an elevation in the endpoint rate in the active versus control treatment arm. Continuous monitoring means that an unblinded statistician has visibility to the treatment assignment of each diagnosed MITT HIV-1 infection as they are determined in real-time, and, after each confirmed HIV-1 infection diagnosis, this statistician notes whether a stopping boundary is reached that indicates that the relative cumulative rate of HIV-1 infection (RR, pooled mAb group/control) exceeds one. If the stopping boundary is met, then the unblinded statistician immediately informs the Chair of the DSMB and the Executive Secretary of the DSMB through secure communication procedures. As such, the potential harm monitoring is in real-time, with a result possible at any time, whereas in contrast the non-efficacy and high efficacy monitoring is conducted only at the 6-monthly scheduled DSMB meetings or at any extra DSMB meetings requested by the DSMB (with exception that the first non-efficacy analysis would be done and reported to the DSMB by secure means prior to a scheduled DSMB meeting if the 67th total primary endpoint event occurs prior to a non-efficacy analysis triggered by at least 45 endpoints by a scheduled DSMB meeting, as described in Table 3).

The potential harm monitoring is done using an exact one-sided binomial test of the null hypothesis $H_0 : p \leq 2/3$ versus the alternative hypothesis $H_1 : p > 2/3$, where p is the probability that an HIV-1-infected participant was assigned to either of the two mAb groups (as compared to being assigned to the control group). The tests start at the 20th total infection through to the infection count at which the non-efficacy/high efficacy monitoring commences, which is a minimum of 45 and is a random variable that depends on the timing of DSMB meetings (this value is referred to as the n^{th} infection). Based on protocol projections we assume that n^* is at most 67, which is useful for setting the critical values of the test. (If the highly unlikely result occurs that n^* exceeds 67, then the first non-efficacy analysis would be conducted based on 67 infections, which would serve the purpose of potential harm monitoring. The number 67 is chosen because that is the infection count at which a point estimate of zero PE would just correspond to an upper nominal 95% confidence bound for PE equal to 0.40; this approach to starting non-efficacy monitoring was suggested by Freidlin, Korn, and Gray (2010).) Each test is performed at a prespecified nominal/unadjusted alpha-level, which may vary over the multiple tests. The alpha-level used for each test is determined indirectly as follows: we must first choose the overall type I error rate we are willing to accept over the course of the monitoring (the overall probability that we reach a stopping boundary during the trial, when the mAb is actually safe, i.e., true $RR = 1$, equivalently $p = 2/3$); and secondly we must choose whether/how to vary the alpha-level from test-to-test. Using

Table 4: Potential harm monitoring stopping boundaries for each AMP trial: One-sided p-value cut-offs for rejecting $H_0 : p \leq 2/3$ in favor of $H_1 : p > 2/3$ with an exact 1-sided binomial test where p is the probability that an HIV-1-infected participant was assigned to one of the two mAb groups

No. of Infections in VRC01 Groups	No. of Infections in Control Groups	Per-Test Type I Error Rate (1-Sided P-value Cut-off)
20	0	0.003
20	1	0.013
20	2	0.018
22	3	0.018
25	4	0.018
28	5	0.018
31	6	0.018
34	7	0.018
37	8	0.018
40	9	0.018
43	10	0.018
45	11	0.018
48	12	0.018
54	13	0.018

these pieces of information we determine the exact alpha-levels to be used for each test.

An overall 1-sided type I error rate of 0.05 is chosen for the family-wise error rate of the multiple hypothesis tests starting at the 20th HIV-1 infection endpoint through to the 67th. This type I error rate is chosen to balance the competing goals of participant safety and preventing false positive results. To prevent stopping too early, perhaps due to spurious results caused by wide sampling variability, stopping prior to the accumulation of 20 total infections was ruled out (the 2:1 mAb:control allocation ratio leads to this choice; in contrast a 1:1 allocation ratio would lead to starting at about 12 total infections). Table 4 shows the potential harm stopping boundaries in terms of the one-sided p-value cut-offs for a selected set of potential harm interim analyses starting at the 20th HIV-1 infection event.

9.2.2 Non-efficacy monitoring

For each AMP trial, the first non-efficacy analysis will be reported to the DSMB at the first scheduled 6-monthly meeting at which at least a total of 45 HIV-1 infection endpoints have occurred, combined over the three study groups. The analysis is based on all HIV-1 infection endpoints up until the time of data lock, and if this number exceeds 67, then the first non-efficacy analysis would be done based on 67 events and the report provided to the

DSMB by secure means prior to the scheduled DSMB meeting (as noted above).

At each non-efficacy interim analysis PE is estimated with a 2-sided 95% nominal confidence interval using the same method as for the final analysis of PE described in Section 8.1. Cumulative prevention efficacy through time t , $PE(t)$, will be estimated at time point t chosen to be the latest possible time point when stable estimation with follow-up data through the Week 80 visit (or earlier if necessary) can be achieved; this is operationalized by defining t as the maximum time point when 150 participants are observed to be at risk for the primary endpoint in each of the placebo and pooled VRC01 groups. The timepoint t will be chosen for evaluation of whether the stopping boundary is crossed or not. All times-to-event will be right-censored at the Week 80 visit or earlier following the operational rules summarized in Table 1. As stated in Table 3, the non-efficacy stopping boundary is defined by the 2-sided upper 95% confidence limit for PE being at 40%, where the 95% CI lying below 40% with the lower 95% confidence limit lying below 0% constitutes meeting the guideline for non-efficacy.

The 2-sided 95% confidence intervals for PE, estimated in the same way as described for the final analysis, are reported for sequential monitoring of PE at every DSMB meeting through to the end of the trial.

In addition, a supplemental analysis will estimate the proportional-hazards PE parameter (defined in (3)) with a 2-sided 95% confidence interval and a two-sided p-value for whether proportional-hazards PE differs from unity, following the same statistical procedures described for the final analysis plan (see Section 8.2).

9.2.2.1 Unblinded conditional power assessment at an interim analysis

Interim monitoring of PE for non-efficacy will be supplemented with an unblinded conditional power assessment using the actual observed control-group incidence, and the following levels of PE in the future data are assumed: $PE = 0\%$, $PE = \widehat{PE}$ in the observed data, and $PE = 60\%$.

9.2.2.2 Estimated prevention efficacy by measured VRC01 neutralization sensitivity

The analyses specified in Section 8.3.1 will be reported at interim analyses that included non-efficacy monitoring.

9.2.3 High efficacy monitoring

The 2-sided 95% confidence interval for PE used for non-efficacy monitoring is also used for high efficacy monitoring, where it is compared to $PE = 70\%$ instead of $PE = 40\%$ as a

stopping boundary. High-efficacy monitoring is conducted at each interim analysis at which non-efficacy analysis is conducted.

9.2.4 Rationale for starting non-efficacy/high efficacy monitoring at at least 45 total infections

Freidlin, Korn, and Gray (2010) suggested beginning non-efficacy monitoring as soon as a point estimate of PE equal to zero would correspond to the nominal 95% confidence interval of a hazard ratio based efficacy parameter under a Cox proportional hazards model just barely ruling out the design alternative (PE = 40% in the AMP trials). This approach implies starting the non-efficacy monitoring at the 67th total infection in each AMP trial. However, based on protocol projections of accrual and incidence, between about 60 and 100 total HIV-1 infection events are expected in each trial, for PE varying over the range 0% to 60%. Therefore it would not be unlikely that no non-efficacy interim analysis would occur if the Freidlin, Korn, and Gray (2010) recommendation were strictly followed. Moreover, a high efficacy analysis would not occur, as its timing is synchronized to the non-efficacy monitoring timing, which could be problematic if the PE is very high. Accordingly, the monitoring starts at at least 45 infections, which is judged to be large enough to have reasonable precision and small enough to make it likely that some non-efficacy/high efficacy interim analyses would occur during the trial. Note that if the first non-efficacy interim analysis occurred at 45 total infections, then stopping for non-efficacy, which would occur if the nominal 2-sided 95% confidence interval lies below 40%, would correspond to a negative PE estimate. This is an advantageous property in that a result of early non-efficacy would be an unambiguous result about absence of prevention efficacy.

9.3 Monitoring of the Use of PrEP

The use of oral FTC/TDF as PrEP (either off-study or provided in the study) may impact study outcomes (e.g., by lowering HIV-1 incidence rendering a loss of study power). Dried blood spot (DBS) samples will be used for assessment of quantitative concentrations of intracellular TFV-DP.

Prevalence of oral FTC/TDF will be reported both as any detectable use and estimated effective use. Estimated percentages of person-years at-risk during any detectable FTC/TDF use and during inferred effective FTC/TDF use will be reported. We summarize how inferred effective use is measured. Current knowledge about PrEP in MSM indicates consistent use of at least 4 doses a week is required to achieve substantial levels of protection. The lower quartile of simulated tenofovir diphosphate (TFV-DP) levels in DBS at 4 doses per week is 719 fmol/punch (Castillo-Mancilla et al., 2013). In iPrEx OLE, the protective levels of TFV-DP in DBS were quantified as 700 fmol/punch (Grant et al., 2014), that is, there were no infections at visits where TFV-DP concentration was 700 fmol per punch or greater. Current knowledge about PrEP in women indicates consistent use of 6–7 doses a week is required to

achieve protection. The lower quartile of simulated TFV-DP levels in DBS at 6 doses per week is 1064 fmol/punch (Castillo-Mancilla et al., 2013). In the HVTN 704/HPTN 085 study we will use 700 fmol/punch as the cut-off to define effective PrEP use based on the lower quartile cited above. For the HVTN 703/HPTN 081 study we will use 1,000 fmol/punch since current knowledge suggests that at least 6 doses of PrEP per week is required for effective PrEP use in women based similarly on the lower quartile. Ongoing work with calibration of DBS from directly observed dosing studies may refine these thresholds. PrEP use measures will be reported by arm to the DSMB; in addition both the OC and the protocol team leadership will see pooled estimates of FTC/TDF use.

HVTN 704/HPTN 085 collects and stores DBS samples at every study visit, whereas HVTN 703/HPTN 081 collects and stores DBS samples at pre-specified DBS sample collection days. The sample collection days can vary by study site; however, it is expected that the collection days will occur once per month. Furthermore, in order to tune the precision of PrEP use estimation, the frequency of collection may be increased. While the storage and collection differs by protocol, the selection of stored samples to assay will be similar. We refer to the method of selecting participant samples for assaying DBS samples for prospective monitoring of PrEP as the DBS sampling plan.

At a given calendar time T (e.g., a fixed date prior to a scheduled DSMB meeting), we are interested in the population-level parameter, percent person-years at-risk for HIV on effective PrEP use between initiation of DBS storage, and time T . Definition of this parameter makes the assumption that we have an assay readout from stored samples that accurately measures effective PrEP use as a binary outcome at the time the sample was drawn; importantly it does not require an accurate measurement of effective PrEP use the day before or for any period of time earlier than the sampling day. In addition to estimating percent person-years on effective PrEP use we define a similar parameter, percent person-years exposed to detectable PrEP using the lower limit of quantitation (LLOQ) of the DBS assay.

Define the target parameter of interest as

$$\Phi(T) = \frac{\int_{T_0}^T p(t) E[Y(t)] dt}{\int_{T_0}^T E[Y(t)] dt}$$

where T_0 is the time since the first person enrolled after DBS storage commenced, $p(t)$ is the percent of participants on effective PrEP use at time $t \in [T_0, T]$, and $E[Y(t)]$ is the expected number of participants with DBS storage at-risk for HIV at time t .

We estimate $\Phi(T)$ based on the binary PrEP use readout from the DBS assay and the DBS sampling plan. Let i ranging from 1 to N index study participants and let j ranging from 1 to M_i index participant serum collection dates that are sampled for assaying. For each sample collected, we have an indicator x_{ij} of effective PrEP use which is only measured if the DBS sampling indicator, Δ_{ij} , is equal to 1. The estimated percent person-years on effective

Table 5: Estimated rates of PrEP use and estimated percent person-years on effective PrEP use

Number of DBS specimens collected over the 1 st batch period	N ₁
Number of DBS specimens assayed over the 1 st batch period	N ₂
Proportion of assayed specimens with TFV-DP above LLOQ (95% CI)	N ₃ /N ₂ (x.xx, x.xx)
Proportion of assayed specimens with TFV-DP above effective use threshold* (95% CI)	N ₄ /N ₂ (x.xx, x.xx)
Percent person years on detectable PrEP through date T=xx (95% CI) [#]	$\widehat{\Phi}(T)_d$ (x.xx, x.xx)
Percent person years on effective PrEP through date T=xx (95% CI) [#]	$\widehat{\Phi}(T)_e$ (x.xx, x.xx)
Repeat through N th batch period	

*threshold defined by study (700 fmol/punch MSM+TG, 1000 fmol/punch sub-Saharan African Women)

[#] $\widehat{\Phi}(T)_d$ is an estimate of the target parameter of interest based on measured TFV-DP above the LLOQ.

Similarly, $\widehat{\Phi}(T)_e$ is based on TFV-DP above the study specific threshold for effective PrEP use.

PrEP use from the initiation of PrEP monitoring time T_0 until time T is defined as

$$\widehat{\Phi}(T) = \frac{\sum_{i=1}^N \sum_{j=1}^{M_i} \Delta_{ij} x_{ij} \pi_{ij}^{-1} P_{ij}}{\sum_{i=1}^N \sum_{j=1}^{M_i} P_{ij}}$$

where the sampling probability, π_{ij} , and person-years, P_{ij} , are defined below.

Let k ranging from 1 to K index the DBS sampling plan collection intervals $[T_0, T_1]$, $(T_1, T_2]$, $\dots$, $(T_{K-1}, T_K]$ where the right endpoint of each interval is a sample collection date (with $T_K \equiv T$) and define $\mathcal{T}_k$ as the k^{th} interval. Let $t_{i1} < t_{i2} < \dots < t_{iM_i}$ be the sampling times in $[T_0, T]$ for the i^{th} participant and define t_{i0} as the maximum of T_0 and the i^{th} participants enrollment time. The DBS sampling plan determines which samples, collectively across participants, will be assayed for PrEP use. Define the set of samples, S_{ij} , as all samples collected during the same collection interval $\mathcal{T}_k$ as the sample i, j . That is, $S_{ij} \equiv \{i', j' | t_{i'j'} \in \mathcal{T}_k \text{ for } k \text{ s.t. } t_{ij} \in \mathcal{T}_k\}$. Define the sampling probability as

$$\pi_{ij} \equiv \frac{\sum_{i', j' \in S_{ij}} \Delta_{i'j'}}{|S_{ij}|}$$

where $|S_{ij}|$ is the number of samples in set S_{ij} . Define person-years, P_{ij} , as $t_{ij} - t_{i(j-1)}$. Note that our parameter of interest can be defined and estimated for the entire study cohort, as well as for sub-regions (e.g., North America for the HVTN 704/HPTN 085 study). We will report bootstrap 95% confidence intervals for $\Phi(T)$.

The same approach is used for point and confidence interval estimation of the percent person-years exposed to detectable PrEP use.

An example of PrEP use report statistics are shown in Table 5.

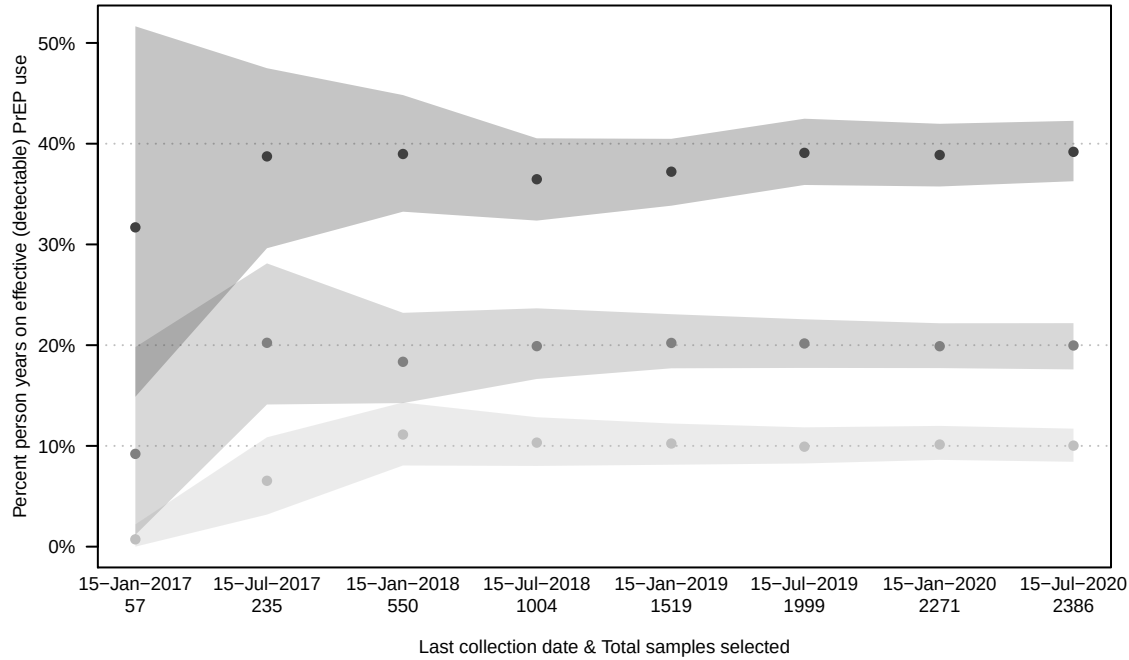


Figure 1: PrEP use Monitoring under three PrEP use scenarios (40%, 20% and 10% per person year) in the HVTN704/085 trial. For 6-monthly intervals shown on the x-axis all samples assayed to date are used to estimate PrEP use prevalence from the beginning of monitoring until that time using the estimator described in Section 8.4. Below each date is the total number of samples that would be assayed according to the simulation study. Estimates are shown as a dots of varying color intensity corresponding to the three PrEP use scenarios. Corresponding color bands are used to show the 95% bootstrap confidence interval for each estimate.

9.3.1 Simulation Study for PrEP Monitoring

A simulation study was conducted to help determine the number of DBS samples that should be collected and assayed a simulation study was run. For a simulated AMP trial, the PrEP monitoring plan was implemented based on the following assumptions: 1) Enrollment falls randomly between Monday and Friday; 2) Follow-up visits follow the visit schedule exactly; 3) Missed visits are distributed uniformly at a rate of 10%; 4) Dropout is 10% per person year based on an exponential distribution; 5) HIV-infection is 3% for HVTN 704/HPTN 085 (or 5.5% for HVTN 703/HPTN 081) per person year based on an exponential distribution; and, 6) Initiation of DBS sample collection begins as of November 1, 2016 in both protocols. PrEP use was simulated at various constant rates among trial participants and participants are assumed to be either on (or off) PrEP during the entire trial. Simulation results for each trial are presented for the number of samples collected spaced at 6 month intervals. The

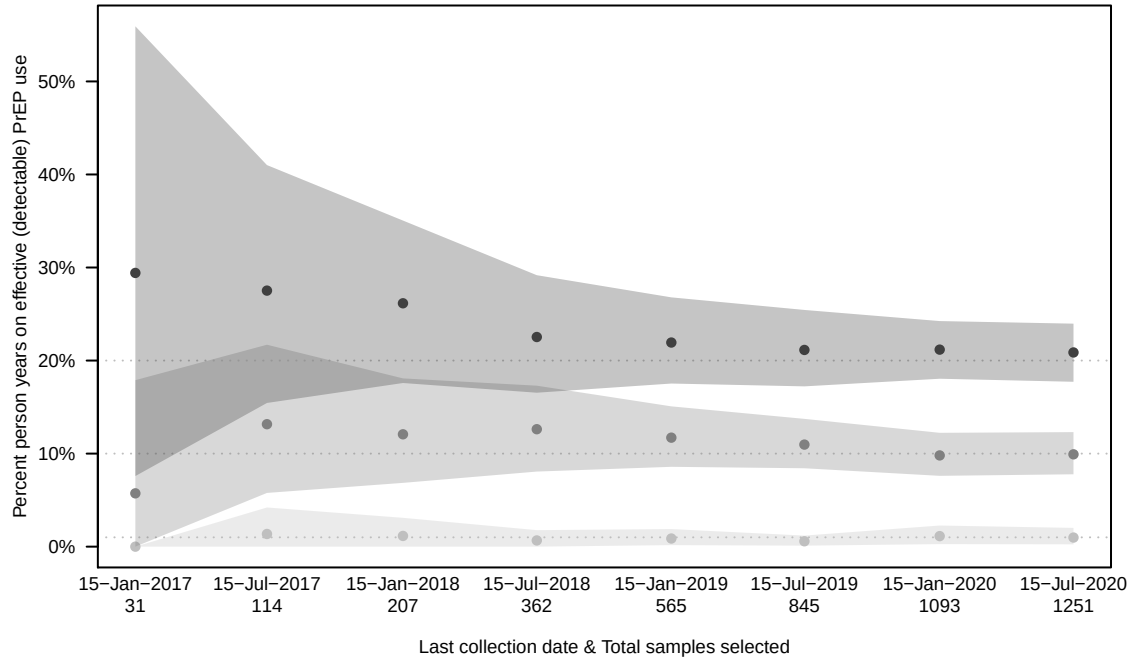


Figure 2: PrEP use Monitoring under three PrEP use scenarios (20%, 10% and 1% per person year) in the HVTN703/081 trial. For 6-monthly intervals shown on the x-axis all samples assayed to date are used to estimate PrEP use prevalence from the beginning of monitoring until that time using the estimator described in Section 8.4. Below each date is the total number of samples that would be assayed according to the simulation study. Estimates are shown as a dots of varying color intensity corresponding to the three PrEP use scenarios. Corresponding color bands are used to show the 95% bootstrap confidence interval for each estimate.

intervals are spaced such that the last collection time point is approximately 3.5 months prior to the next DSMB meeting to allow the intracellular TFV-DP assay to be run and a report generated. In this simulation, all samples collected per protocol HVTN703/HPTN081 version 2.0 would be assayed. For the HVTN704/HPTN085 trial, all samples collected the clinic business day closest to the 15th of each month would be assayed. Simulation results are shown in Figures 2 and 1.

The simulation study results show that by the time 200 samples have been selected the confidence intervals around the estimate of PrEP use are reasonably tight and by the time 500 samples have been selected the extra gain in precision as more samples are assayed becomes limited. However, continuing to assay samples over the course of the trial will allow estimation of temporal trends in PrEP use. The simulation also shows that when PrEP prevalence is very low the bootstrap confidence interval is unlikely to provide proper

coverage.

9.4 Monitoring for Futility to Assess Prevention Efficacy

The objective of monitoring the trial for futility to assess PE is to monitor progress toward the minimal needed target number of treatment arm-pooled HIV-1 primary endpoint infections by the Week 80 visit in the MITT cohort. Two targets are monitored for:

1. the total number of HIV-1 infections needed to achieve the planned 90% power to detect $PE = 60\%$, and
2. the total number of HIV-1 infections needed to achieve 50% power to detect $PE = 60\%$,

each using a 1-sided 0.025-level Wald test of $H_0 : PE \leq 0\%$ against $H_1 : PE > 0\%$, assuming proportional hazards of HIV-1 infection in the pooled VRC01 and control groups. The target numbers in 1. and 2. are 57 and 21, respectively (calculated by solving equation (1) in Schoenfeld (1983)). The rationale for considering the two targets is as follows: (i) if the trial cannot achieve the planned 90% power to detect $PE = 60\%$, considerations about enrollment modification or expansion are warranted, and (ii) if the trial cannot achieve even 50% power to detect $PE = 60\%$, considerations about completing the trial early for futility to assess PE are warranted.

Two versions of the futility monitoring report will be generated. A report provided to the DSMB will be included in 6-monthly closed DSMB reports, starting in November 2017 for HVTN 703/HPTN 081 and in April 2018 for HVTN 704/HPTN 085, and will report:

- (a) the estimated distribution of the total (i.e., treatment arm-pooled) number of HIV-1 infections, with corresponding power to reject $H_0 : PE \leq 0\%$ using a 1-sided 0.025-level Wald test under the alternative hypothesis $PE = 60\%$ throughout the trial,
- (b) the estimated probability that the total number of HIV-1 infections is ≥ 57 (target 1) with 95% credible intervals,
- (c) the estimated probability that the total number of HIV-1 infections is ≥ 21 (target 2) with 95% credible intervals,
- (d) the estimated distribution of the number of HIV-1 infections in each of the three treatment arms.

The distributions in (a) and (d) will also be summarized by the mean number of HIV-1 infections with a Wald 95% confidence interval. The estimation procedures for (a)–(d) will be conducted under each of the following three scenarios:

- (i) the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that $PE = 60\%$ (the design alternative),
- (ii) the treatment arm-pooled infection rate in (a)–(c) and the three treatment arm-specific infection rates in (d) used for generating future data are based on a Bayesian model and the prior assumption that $PE = 0\%$ (the null hypothesis), and
- (iii) the treatment arm-pooled infection rate in (a)–(c) used for generating future data is based on a Bayesian model and the prior assumption that the infection rate equals the observed to-date infection rate.

The reason for conducting the estimation procedure under (i)–(iii) is that the purpose of the results for the 57 endpoint target (b) is to trigger considerations about enrollment modifications, whereas the purpose of the results for the 21 endpoint target (c) is to trigger considerations about early trial completion due to futility, where it is desired to reach a guideline based on (b) more easily/readily than a guideline based on (c). Accordingly, the results for (b) are interpreted focusing on the prior of $PE = 60\%$ (i.e., scenario (i)), which makes it more likely to reach a guideline than the prior of $PE = 0\%$, and the results for (c) are interpreted focusing on the prior of $PE = 0\%$ (i.e., scenario (ii)), which makes it less likely to reach a guideline than the prior of $PE = 60\%$. Results for (b) and (c) based on carrying forward the observed to-date infection rate in scenario (iii) provide additional guidance to the DSMB regarding considerations about enrollment modification or early trial completion.

Furthermore, a treatment-blinded report will be generated for distribution to the Leadership Group before each DSMB meeting takes place and will report estimates listed in (a)–(c) above calculated based only on treatment-blinded data in scenarios (i)–(iii). The reported results pertaining to estimates (a)–(c) under scenarios (i)–(iii) will be identical to those in the DSMB report.

While it is the primary responsibility of the Leadership Group to make decisions regarding trial operations and modifications based on the monitoring of treatment-blinded primary endpoints, given the resource issues involved, DSMB review is also needed because issues of scientific integrity are also involved. More specifically, the DSMB can evaluate the progress toward primary endpoint targets in the context of the treatment-unblinded data, and based on this review may recommend to the Leadership Group to complete the trial early due to reaching a guideline for futility to assess PE (specified below).

The monitoring for futility to assess PE includes the following guidelines for trial modifications:

- **Guideline for enrollment modifications.** If, in the $PE = 60\%$ scenario for the prior distribution in (i), the estimated probability of reaching at least 57 total infections is less than 25%, the Leadership Group may consider enrollment modifications with the intention to be able to conduct the primary PE analysis with adequate power.

- **Guideline for futility.** If, in the $PE = 0\%$ scenario for the prior distribution in (ii), the estimated probability of reaching at least 21 total infections is less than 25%, the DSMB may recommend completing the trial early based on the inability to conduct the primary PE analysis with adequate power. However, since this is a proof-of-concept trial, a high bar is desired for completing the trial early for futility, and therefore if this event occurs yet the non-efficacy monitoring has not started or the non-efficacy boundary has not been reached, then this guideline for futility also requires that the estimated PE for the pooled VRC01 vs. control arm is $< 30\%$ and the estimated PE for the VRC01 30 mg/kg vs. control arm is $< 30\%$.

If enrollment is incomplete at the time of an interim futility analysis, then the outlined estimation procedures will use the average observed enrollment rate in approximately the last 6 months for generating future enrollment data. A Bayesian approach will be used for generating future HIV-1 incidence data, conditional on observed data to-date. More specifically, the estimates in (a)–(c) will condition on the observed to-date treatment arm-pooled HIV-1 incidence rate, whereas the estimates in (d) will condition on the three observed to-date treatment arm-specific HIV-1 incidence rates. All estimates in (a)–(d) will also use the observed to-date treatment arm-pooled dropout rate for generating future dropout data. Further details of these calculations, including the prior distributions, are described in Section 9.4.1.

If, at any time, these guidelines for futility to assess PE are met and yet it appears that value exists in continuing the trial, the statisticians will provide the DSMB and the Leadership Group with additional information, as appropriate, for use in their consideration of whether to recommend early trial completion.

9.4.1 Estimation of the number of HIV-1 infection endpoints at an interim analysis

The method for estimating the probability distribution of the number of HIV-1 infection endpoints by the Week 80 visit is based on the following approach to simulating this trial. The trial is modeled as a combination of three processes—enrollment, dropout, and HIV-1 infection—and a large number of trials is simulated. The three processes are assumed to be independent, and their distributions are taken to be Poisson, exponential, and exponential, respectively. Data are generated at the level of the individual participant, such that, for each participant, we obtain an enrollment time, an (underlying true) infection time, and a dropout time. Only the minimum of the infection and dropout times is observable, and the average value for this minimum is beyond the duration of the trial, such that neither event will be observed for most participants.

In the absence of observed trial data, the treatment arm-pooled as well as the treatment arm-specific parameters for the infection and dropout processes are chosen to match our pre-trial assumptions about these rates. In addition, the infection rate considers both the

design alternative of $PE = 60\%$ and the null hypothesis of $PE = 0\%$ in the calculation of the total and treatment arm-specific numbers of endpoints. More specifically, in HVTN 704/HPTN 085, treatment arm-pooled calculations in (a)–(c) assume

- pooled infection rate ($PE = 60\%$ scenario): $(1/3) \times 0.03 + (2/3) \times 0.4 \times 0.03 = 0.018$ infections/person-year at-risk, and
- pooled infection rate ($PE = 0\%$ scenario): 0.03 infections/person-year at-risk,

and, in HVTN 703/HPTN 081,

- pooled infection rate ($PE = 60\%$ scenario): $(1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ infections/person-year at-risk, and
- pooled infection rate ($PE = 0\%$ scenario): 0.055 infections/person-year at-risk.

Both trials assume a treatment arm-pooled dropout rate of 0.10 dropouts/person-year at-risk.

In HVTN 704/HPTN 085, treatment arm-specific calculations in (d) assume

- infection rate in the control arm: 0.03 infections/person-year at-risk,
- infection rate in each VRC01 arm ($PE = 60\%$ scenario): $0.4 \times 0.03 = 0.012$ infections/person-year at-risk, and
- infection rate in each VRC01 arm ($PE = 0\%$ scenario): 0.03 infections/person-year at-risk,

and, in HVTN 703/HPTN 081,

- infection rate in the control arm: 0.055 infections/person-year at-risk,
- infection rate in each VRC01 arm ($PE = 60\%$ scenario): $0.4 \times 0.055 = 0.022$ infections/person-year at-risk, and
- infection rate in each VRC01 arm ($PE = 0\%$ scenario): 0.055 infections/person-year at-risk.

In the absence of observed data, in both trials and each of the three treatment arms, the dropout rate is assumed to be 0.10 dropouts/person-year at-risk.

The first step in simulating each trial is to enroll a certain number of participants per week according to a random draw from a Poisson distribution with rate parameter as listed above. Enrollment continues week-by-week until a total of 2700 participants in HVTN

704/HPTN 085 or 1900 participants in HVTN 703/HPTN 081 is reached. Second, each participant is assigned an exact enrollment day, uniformly distributed within their enrollment week. Following enrollment, the infection and dropout times are drawn from their respective exponential distributions, and the lesser of the two is recorded as occurring at the given time (possibly outside the time-window of the trial). We consider dropout events to have occurred at the dropout time (in weeks) that was generated (assuming it was less than the infection time). For participants who become HIV-1 infected, we record their time of diagnosis as the time of the first study visit following the true infection time. It is this time of diagnosis that we observe for infected participants.

A modification of the above procedure for simulating an efficacy trial is used for estimating metrics of futility to assess PE at a given interim analysis. The modification entails using the observed trial data to estimate parameters of the processes, rather than relying entirely on pre-trial assumptions. In particular:

- enrollment rate: if enrollment is incomplete, estimated based on the treatment arm-pooled rate observed in approximately the last 6 months in the study,
- infection rate: drawn from a posterior distribution of the infection rate formed by combining the observed data with our prior specification about the infection rate based on the pre-trial assumptions, and
- dropout rate: estimated based on the treatment arm-pooled rate observed to date.

The rationale for a Bayesian approach for the infection rate (see Section 9.4.2 for details) is to help stabilize the infection rate early in the trial when insufficient time will have passed to accrue many infections. If we were to rely solely on the observed infections, we might by chance obtain very low rates, which would lead to an unrealistic prediction of the number of endpoints.

We consider three different gamma prior distributions for the infection rate in each of scenarios (i)–(iii) reflecting different weights assigned to the prior distribution (see Section 9.4.2 for details). Gamma distributions are considered because they are conjugate to the exponential distribution used for generating future infection data.

At a given interim analysis, 10^5 trials are simulated using the above procedure and treatment arm-pooled infection and dropout rates for estimates in (a)–(c). Separately, another set of 10^5 trials is simulated using the above procedure, treatment arm-specific infection rates, and the treatment arm-pooled dropout rate for estimates in (d). Each of these trials yields a projected number of infections by the Week 80 visit. These projected numbers of infections from each trial will be used to estimate the entire distribution of the number of infections. The probability of reaching at least the target number of infections will be estimated as the proportion of trials with the projected number of infections greater than or equal to the target.

Figures on enrollment, HIV-1 incidence and dropout over time will also be included to aid interpretation of the results.

9.4.2 A Bayesian model for the HIV-1 incidence rate in estimation of the number of HIV-1 infection endpoints at an interim analysis

Let n_k and T_k denote, respectively, the infection count and the observed total person-time at risk at the time of the k -th futility analysis, pooling over all treatment arms. Additionally, let T^* denote the estimated total person-time at risk for the primary efficacy analysis. Let the prior distribution of the pooled HIV-1 incidence rate p be $\text{Ga}(\alpha, \beta)$ parametrized such that the prior mean $E p = \alpha/\beta$ (the same Bayesian method applies to the treatment arm-specific HIV-1 incidence rate).

Generally, assuming that, conditional on p , the times to infection follow $\text{Exp}(p)$, the posterior mean of p at the time of the k -th analysis equals

$$\begin{aligned} E[p | \text{data}] &= \frac{\alpha + n_k}{\beta + T_k} \\ &= \frac{\alpha}{\beta} \frac{\beta}{\beta + T_k} + \frac{n_k}{T_k} \frac{T_k}{\beta + T_k}, \end{aligned} \quad (4)$$

i.e., the posterior mean can be interpreted as a convex combination of the prior mean and the observed incidence rate. For a given $\beta > 0$, the weight on the prior mean at the first analysis depends on the accumulated person-time at risk (T_1), and the weight will decrease in subsequent analyses because $\beta/(\beta + T_k)$ is a decreasing function of T_k , which is a desirable Bayesian property.

In order to identify α and β , it is desirable that the prior mean equals the pre-trial assumed treatment arm-pooled incidence rate p^* (e.g., under $PE = 60\%$, $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ in HVTN 703/HPTN 081), i.e.,

$$\frac{\alpha}{\beta} = p^*.$$

Furthermore, we propose to consider three values of β that correspond to the weights $w = \frac{1}{2}$, $\frac{1}{3}$ and $\frac{1}{4}$ on the prior mean at the time when 50% of the estimated total person-time at risk has been accumulated, i.e., for each value of w , β is defined as the solution to the equation

$$\frac{\beta}{\beta + T^*/2} = w.$$

It follows that

$$\beta = \beta(w, T^*) = \frac{wT^*}{2(1-w)},$$

and the estimation of T^* is described in Section 9.4.2.1. For $w = \frac{1}{2}$, $\frac{1}{3}$ and $\frac{1}{4}$, we obtain $\beta = \frac{T^*}{2}$, $\frac{T^*}{4}$, and $\frac{T^*}{6}$, respectively.

At the k -th futility analysis and for each of the three values of β , we will sample the HIV-1 incidence rate from $\text{Ga}(\alpha + n_k, \beta + T_k)$ for generating future data and report the weight $\frac{\beta}{\beta + T_k}$ on the prior mean in the convex combination (4).

9.4.2.1 Estimation of the total person-years at risk (T^*)

We will use HVTN 703/HPTN 081 to illustrate the calculation. In this trial, the total target sample size is $N = 1900$, the duration of follow-up per participant is $\tau = 80/52$ years, the pre-trial assumed dropout rate is $d^* = 0.1$ dropouts per person-year at risk (PYR), and, in the $PE = 60\%$ scenario, the pre-trial assumed treatment arm-pooled HIV-1 incidence rate is $p^* = (1/3) \times 0.055 + (2/3) \times 0.4 \times 0.055 = 0.033$ cases per PYR.

We consider the standard right-censored failure time analysis framework. Denoting the failure and censoring times as T and C , respectively, we assume that T is independent of C , $T \sim \text{Exp}(p^*)$, and $C \sim \text{Exp}(d^*)$. It follows that $X := \min(T, C) \sim \text{Exp}(p^* + d^*)$ and

$$\begin{aligned} T^* &= N \times E[\min(X, \tau)] \\ &= N \times \{E[X \mid X \leq \tau] P(X \leq \tau) + \tau P(X > \tau)\} \\ &= N \times \left\{ (p^* + d^*) \int_0^\tau x \exp^{-(p^* + d^*)x} dx + \tau \exp^{-(p^* + d^*)\tau} \right\} \\ &= N \times \frac{1 - \exp^{-(p^* + d^*)\tau}}{p^* + d^*}. \end{aligned}$$

In HVTN 703/HPTN 081, this amounts to $T^* = 2643.42$ PYRs. For comparison, if all N participants were followed for τ years, the total PYRs would be $N\tau = 2923.08$ years.

Subsequently, for $T^* = 2643.42$ PYRs, if $T_1 = 0.2 T^*$, the weights $\frac{\beta}{\beta + T_1}$ on the prior mean at the first futility analysis corresponding to $w = \frac{1}{2}$, $\frac{1}{3}$, and $\frac{1}{4}$ are 0.71, 0.56, 0.45, respectively. If $T_1 = 0.3 T^*$, the respective weights on the prior mean are 0.63, 0.45, and 0.36.

9.5 Monitoring for Performance Standards of Quality of Trial Conduct

The protocol team and study investigators will have performance standards regarding the quality of trial conduct in addition to the study endpoint rate. Some of these use standard metrics detailed in the Network Evaluation Metrics and Standards document, whereas others are specific to the AMP trials. Some of these standards will relate to achievement of targeted levels of:

1. participant enrollment into the trial (targets based on protocol assumptions);

2. retention of participants (target 5% annual dropout or less, with minimally acceptable level of no more than 10% annual dropout; also target 90% visit attendance among participants under follow-up [NEC standard]).
3. adherence to receipt of infusions (target 90% of infusions received, with minimally acceptable level of 70% of infusions received).
4. quality and timeliness of HIV-1 diagnostic testing.
5. quality and timeliness of data collected on case report forms.

Appendix A describes the output that is used to evaluate items 1 (Figure 17), 2 (Table 5A and Figure 1), and 3 (Table 5B and Figure 3), and Section 9.1 provides additional information about 3 in terms of the feasibility check monitoring.

9.5.1 Expanded details for reporting on item 4: quality and timeliness of HIV-1 diagnostic testing

1. **Timeliness:** Turnaround time from blood collection to diagnostic reporting is summarized. This process monitors the site, the site-processing lab, the shipping company and the actual diagnostics lab. In addition the turnaround time from arrival in the lab to reporting is monitored, which isolates the turnaround time to the lab.
2. **Quality:** No additional monitoring for HIV-1 diagnostic quality is done beyond the fact that the labs participate in CAP and VQA and they are all audited annually by DAIDS.

9.5.2 Expanded details for reporting on item 5: quality and timeliness of data collected on case report forms

This reporting will use NEC standard metrics, as detailed in the Network Evaluation Metrics and Standards document (pages 12-14). In summary, the reporting outputs are as follows:

1. **For Quality:** For **QC Rate**, the standard metric for satisfactory quality is < 10 QCs per 100 pages. The denominator for this metric includes the total number of pages entered in the database during the time period. For refaxes, only the most recent page faxed is included. All CRF pages faxed to SCHARP are included in this calculation. Total CRF pages are labeled (Total Pages1) in the DMQ table.

For **QC Resolution**, the standard metric is > 80% of QCs resolved in < 7 calendar days.

For **Percent EDCd**, note that quality tends to be higher when pages are submitted via EDC (real time validation, faster submissions, etc), and this metric incentivizes sites to use EDC.

2. **Timeliness:** The standard metric for CRF Submission Rate (% pages faxed/EDCd on time) is $> 90\%$ of pages submitted within < 4 calendar days. The denominator for this metric is not total pages, as it excludes pages that, according to study operations, may not be completed and/or faxed immediately following a study visit (e.g., screening visit forms). Log-based forms are also not included. For refaxes, only the initial page faxed is included. Only time-critical CRF forms are calculated. Screening and log based forms are excluded. CRFs included in this calculation are labeled (Total Pages2). HIV test results are excluded.

The DSMB and the leadership of the AMP trials will monitor whether the trials are achieving at least minimally acceptable levels of key performance standards. The DSMB will make recommendations to improve areas that are deficient. Termination of a trial would be considered if it appears unlikely that minimally acceptable performance will be achieved.

10 Statistical Software

All analyses described in this SAP will be conducted in *R*.

11 Roles of Study Statisticians

HVTN SDMC statisticians will be blinded or unblinded to treatment group. During protocol development and after primary follow-up is completed, there will be no distinction between the roles; both types of statisticians will be responsible for designing and analyzing the study. During the primary follow-up period, however, only the treatment-unblinded statistician(s) will see interim data broken down by treatment group. Their role will be to conduct the interim monitoring and to produce and present reports on accruing data to the study DSMB. During the primary follow-up period, treatment-blinded statisticians will see only the interim data pooled across study groups. This way, treatment-blinded statisticians can assist protocol leadership in making decisions about modifications to the protocol without being influenced by interim efficacy results.

Appendix A

Mock tables and figures for the DSMB Closed Report are included below. The Closed Report summarizes trial information pooled across the treatment groups (labeled Total) and by masked treatment assignment (labeled A, B, and C). At the request of the DSMB, protocol statisticians will unmask treatment labels. A subset of these tables and figures will

form the Open Report, in which trial information is reported pooled across the treatment groups.

DRAFT

HVTN xxx/ HPTN xxx

**Data and Safety Monitoring Board (DSMB)
CLOSED Report**

Tables and Figures

Table 1. Disposition of Study Participants by Treatment Assignment
Table 2. Baseline Participant Characteristics by Treatment Assignment
Table 3. Baseline Risk Behaviors by Treatment Assignment
Table 4. Study Status and Reasons for Early Study Termination by Treatment Assignment
Table 5A. Visit Retention by Treatment Assignment
Table 5B. Adherence by Treatment Assignment
Table 6. Permanent Discontinuation of Infusions by Treatment Assignment
Figure 1. Study Continuation (Time to Discontinuation) by Treatment Assignment
Figure 2. Boxplot for Time Between Infusions by Treatment Assignment
Figure 3. Sample of Adherence Patterns over Study Time by Treatment Assignment
Table 7A. Maximum Local Reactogenicity Summary by Treatment Assignment
Table 7B. Maximum Systemic Reactogenicity Summary by Treatment Assignment
Figure 4. Maximum Local Reactogenicity, by Treatment Assignment
Figure 5: Maximum Systemic Reactogenicity, by Treatment Assignment
Table 8. Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC) Listed by Treatment Assignment, Participant and Decreasing Severity
Table 9. Adverse Events (AEs) by System Organ Class and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 10. Grade 3–5 Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 11. Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment Sorted by Decreasing Frequency
Table 12. Adverse Events (AEs) Related to Study Product by High Level Term and Treatment Assignment
Table 13A. Distribution of Safety Laboratory Values, by Treatment Assignment
Table 13B. Safety Laboratory Values Meeting Grade 1 AE Criteria or Above, by Treatment Assignment
Table 14. Pregnancy Listing
Figure 6. Boxplot for ALT by Infusion Visit and Treatment Assignment
Figure 7. Boxplot for Hemoglobin by Infusion Visit and Treatment Assignment

Figure 8. Boxplot for Platelets by Infusion Visit and Treatment Assignment
Figure 9. Boxplot for WBC by Infusion Visit and Treatment Assignment
Figure 10. Boxplot for Neutrophil Count by Infusion Visit and Treatment Assignment
Figure 11. Boxplot for Lymphocyte Count by Infusion Visit and Treatment Assignment
Figure 12. Boxplot for Creatinine by Infusion Visit and Treatment Assignment
Figure 13. Confirmation/Adjudication Process for HIV Infections
Table 15. HIV Adjudication Timeline
Table 16. HIV Infections
Figure 14. Cumulative HIV Incidence Among All MITT Participants by Treatment Arm
Table 17. ART Initiation among MITT Infected Participants
Figure 15. Viral Load Over Time Among All Infected MITT Participants
Figure 16. Cumulative Number of Infusions Missed by Infusion Visit for All Infected MITT Participants
Table 18a. Visit Retention for All MITT Pre-Trial HIV-1 and HIV-2 Infected Participants by Treatment Assignment
Table 18b. Visit Retention for All MITT Post-Trial HIV-1 Infected Participants by Treatment Assignment
Figure 17. Cumulative Enrollment

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 1. Disposition of Study Participants by Treatment Assignment^

	Total	A	B	C
Number Randomized	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Enrolled	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pending Enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Number Enrolled*	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
On Study (in Primary Follow-Up)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Primary Follow-up	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Study Termination	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

^ Enrolled implies receipt of the first study product

* Primary Follow-Up is 92 weeks for uninfected participants and 24-weeks post-diagnosis for infected participants

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 2. Baseline Participant Characteristics by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Gender Identity				
Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Male	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Transgender Female	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Gender Queer	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Age (years)				
18 - 20	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
21 - 30	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
31 - 40	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
41 - 50	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median	xx	Xx	xx	xx
Min, Max	xx - xx	xx – xx	xx - xx	xx - xx
Race				
White	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Black or African American	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Asian	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Hawaiian/Pacific Islander	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Native Am./Alaska Native	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other Race	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Multi-racial	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missing	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

NOTE: Participants may self-report more than 1 gender identity, thus numbers and percentages may total to more than 100%

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Number Sex Partners in the Last Month				
0	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
3-4	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
>=5	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Median	xxx	xxx	xxx	xxx
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Had an HIV+ Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Receptive Vaginal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Insertive Vaginal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Insertive Anal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unprotected Receptive Anal Sex with a Partner				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Exchange of Sex for Money/Gifts				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Alcohol Use				
Never	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Monthly or less	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2-4 times a month	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
2-3 times a week	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
4 or more times a week	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Prefer not to answer				
Injection Drug Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Marijuana Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Crack cocaine use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Powder cocaine use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Amphetamine/Methamphetamine/Crystal Meth Use				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Methaqualone or Mandrax Use?				
Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 3. Baseline Risk Behaviors by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Heroin, Prescription Pain Killers/Medications Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
MDMA or Ecstasy Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Popper Use Yes	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 4. Study Status and Reasons for Early Study Termination by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)	xxx (100.0%)
Status				
In Infusion Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
In FU, Completed Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
In FU, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed FU and Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed FU, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination, Completed Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination, Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons for Early Termination	(n=x)	(n=x)	(n=x)	(n=x)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant refused	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to adhere to visit schedule	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant relocated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Unable to contact	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Investigator decision	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Inappropriate enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Duplicate screening/enrollment	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early study closure	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant incarcerated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Study product infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination Due to an Adverse Experience	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Early Termination Due to Study Product infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 5A. Visit Retention by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx	xxx	xxx	xxx
Week 4 / 28 days post Infusion 1				
Expected and/or Completed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently discontinued infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
Week 92 / 140 days Post Infusion 10				
Expected and/or Completed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently discontinued infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Post-infusion visits are not expected if the infusion visit was not done.

Retention = # Participants who completed the visit / # Participants expected for and/or completed the visit.

A visit is considered expected if the participant is in Schedule 1 at the time of the visit and the visit window has closed.

A visit is considered completed once the Post-Enrollment IV Infusion Administration or Specimen Collection form is entered in the study database.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 5B. Infusion Adherence by Treatment Assignment

	Total	A	B	C
Total Enrolled	xxx	xxx	xxx	xxx
Week 0 / Infusion 1				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 8 / Infusion 2				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
Week 72 / Infusion 10				
Retained	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Received Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed Infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Retained = # Participants who completed the visit

A visit is considered completed once the Post-Enrollment IV Infusion Administration or Specimen Collection form is entered in the study database

A participant has received infusion once the Post-Enrollment IV Infusion Administration is entered in the study database

.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

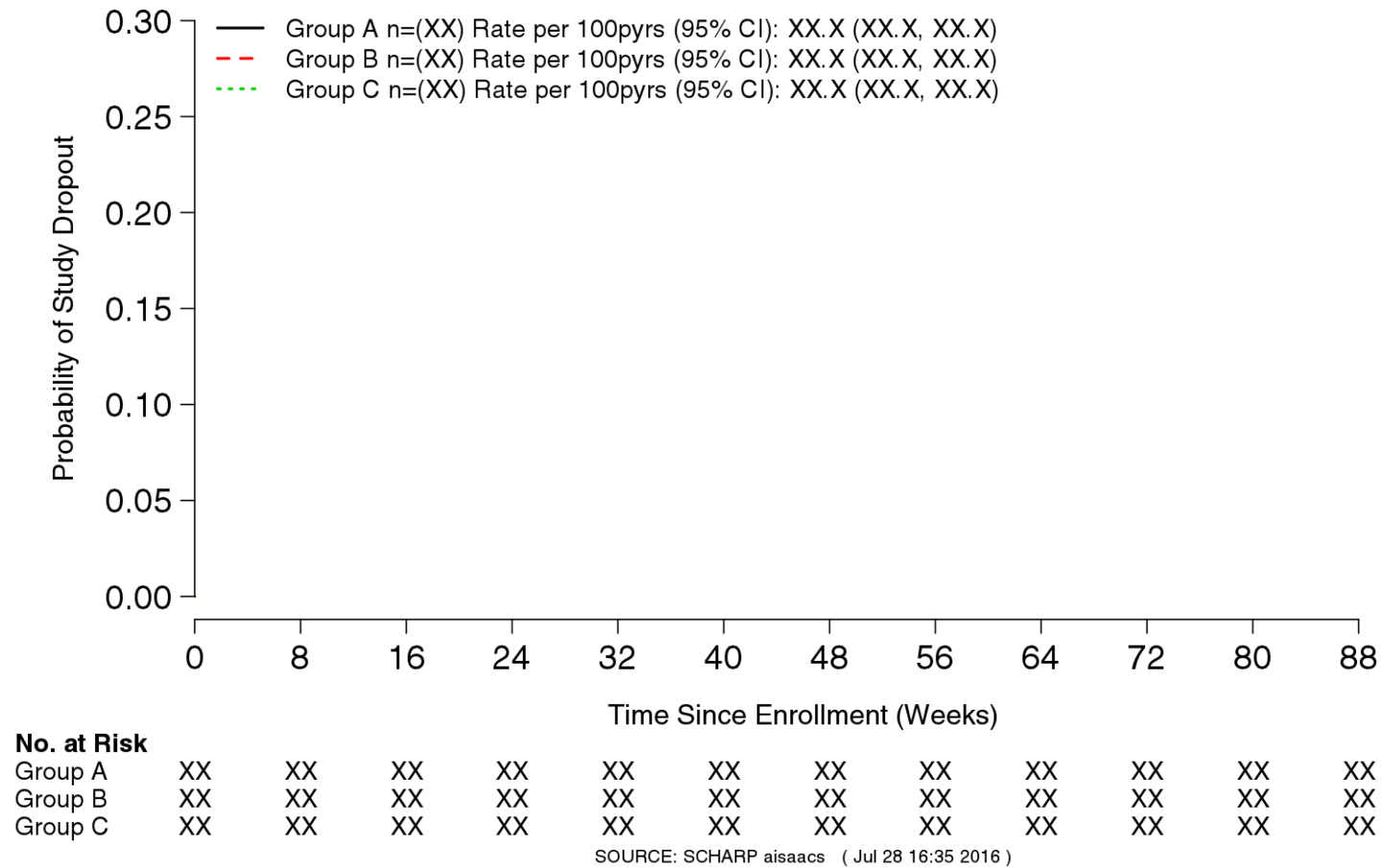
Data Cutoff date:[Date].

Table 6. Permanent Discontinuation of Infusions by Treatment Assignment

	Total	A	B	C
Infusion Status				
In Infusion Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Completed Infusions Phase	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Permanently Discontinued Infusions	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reasons For Discontinuation	xxx	xxx	xxx	xxx
Pregnancy	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
HIV infection	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Death	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Clinical event	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Reactogenicity symptom	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Investigator reason	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Participant refused study product infusion	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Co-enrollment in a study	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Two reactive HIV tests	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Other	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

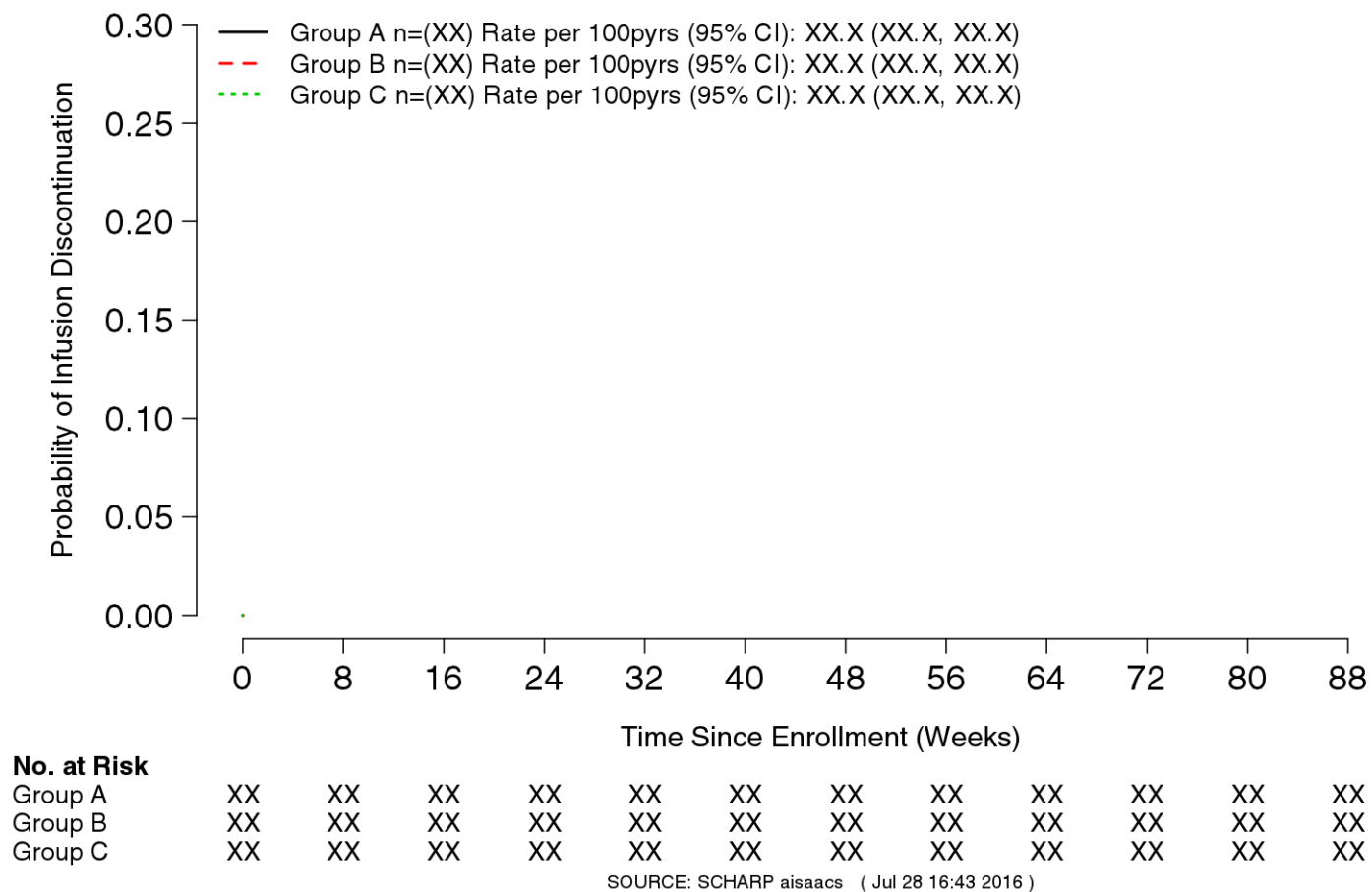
HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 1A. Cumulative Incidence of Dropout by Treatment Assignment



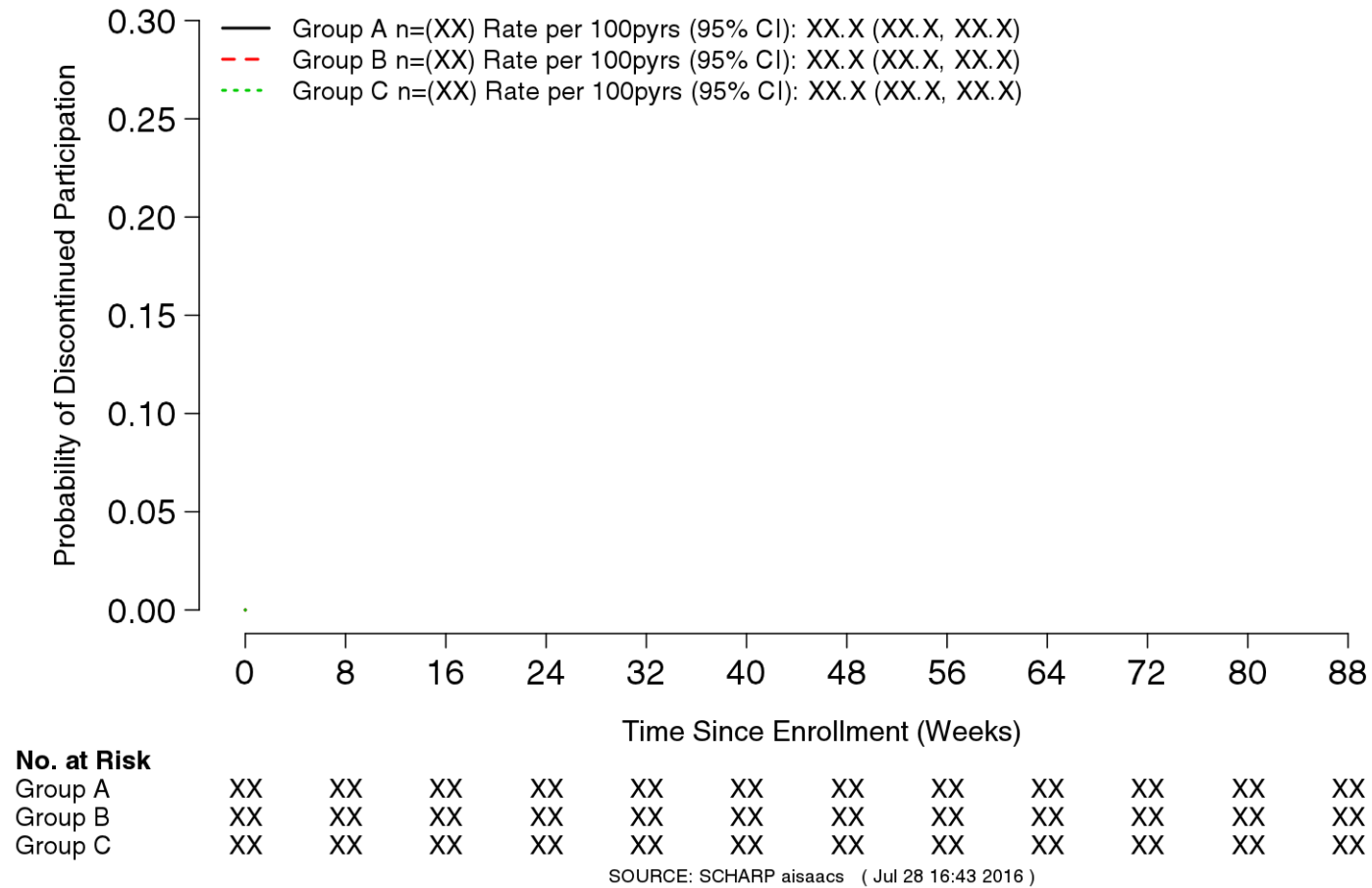
HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 1B. Cumulative Incidence of Infusion Discontinuation by Treatment Assignment



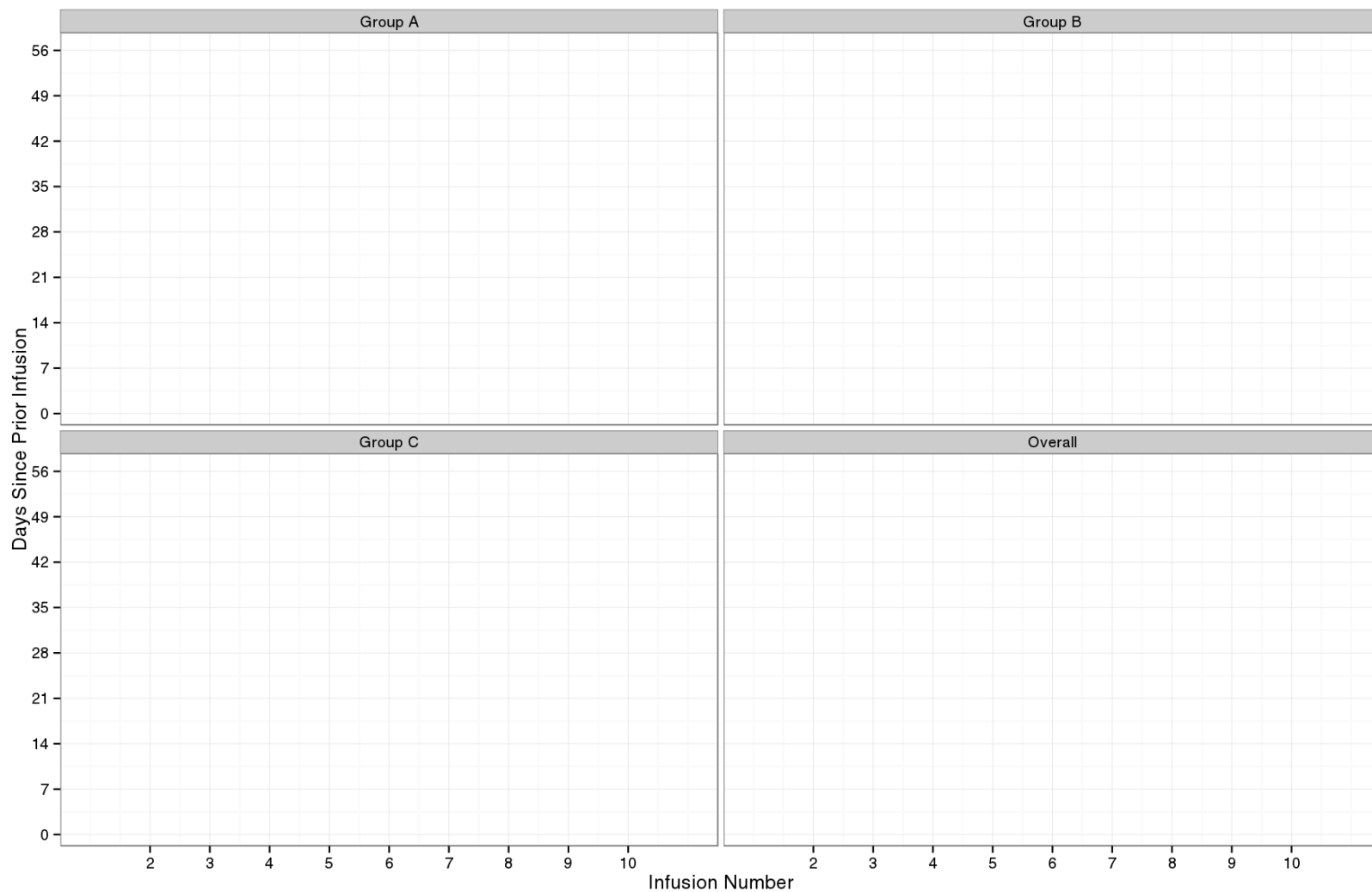
HVTNxxx/HPTNxxx:
 Closed DSMB Report for DSMB meeting on [Date].
 Data Cutoff date:[Date].

Figure 1C. Cumulative Incidence of Discontinued Participation (Dropout or Infusion Discontinuation) by Treatment Assignment



HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Figure 2. Boxplot for Time Between Infusions by Treatment Assignment

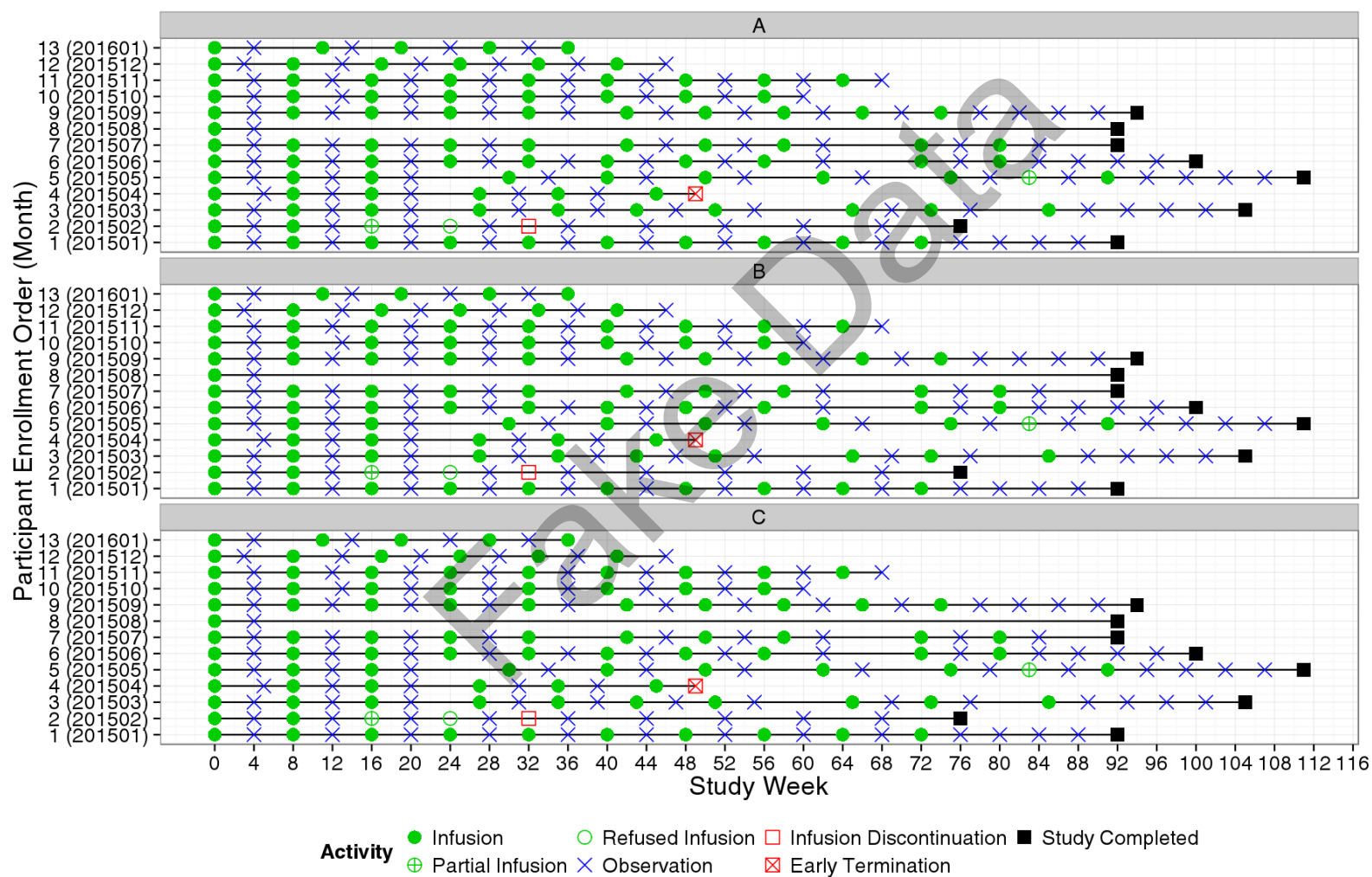


HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 3. Sample of Adherence Patterns over Study Time by Treatment Assignment



HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 7A. Maximum Local Reactogenicity Summary By Treatment Assignment

	Total		A		B		C	
Number Infused	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Tenderness								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Pain and/or Tenderness								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Erythema								
None or not gradeable	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
6.25 to < 25 cm ² or 2.5 to <5 cm single dim (Gr 1)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
25 to < 100 cm ² or 5 to <10 cm single dim (Gr2)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
>= 100 cm ² or >= 10 cm single dim or severe complication (Gr 3)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
> Potentially life threatening complication (Gr 4)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

NOTE: Events are noted in the category of highest severity grade reported.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 7B. Maximum Systemic Reactogenicity Summary By Treatment Assignment

	Total		A		B		C	
Number Infused	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Malaise and/or Fatigue								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Myalgia								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Headache								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Nausea								
None	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Mild	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Potentially Life-Threatening	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

Events are noted in the category of highest severity grade reported.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 4. Maximum Local Reactogenicity, by Treatment Assignment

Boxplots of local reactogenicity events defined as specific surveyed adverse events that are commonly associated with infusion administration and that have an onset within 3 days following an infusion. Local reactogenicity events assessed in this study are: local pain to the infusion site, local tenderness to the infusion site, erythema at the infusion site, and induration/swelling at the infusion site. Severity definitions are based on The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0 (January 2010).

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 5: Maximum Systemic Reactogenicity, by Treatment Assignment

Boxplots of systemic reactogenicity events defined as specific surveyed adverse events that are commonly associated with infusion administration and that have an onset within 3 days following an infusion. Systemic reactogenicity events are: malaise and/or fatigue, myalgia, headache, nausea, vomiting, chills, arthralgia and body temperature. Severity definitions are based on The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 2.0 (January 2010).

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 8. Expedited Adverse Experiences (EAEs) Reported to the Regulatory Support Center (RSC) by Treatment Assignment, Participant and Decreasing Severity NOTE: * in column 'Non Rept.' indicates non-reportable EAE by DAIDS criteria, as determined by RSC.

Trt.	Publication ID	Severity	EAE Number	Adverse Experience	Onset Date	Relation to Study Product	Medical Officer's Relation to Study Product	Number of Previous Infusions	Days Since Last Infusion	Non Reportable
A	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
B	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
C	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	
	XXX-XXXX	text	XXXXXX	text	dd-MMM-yyyy	text	text	X	XX	

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 9. Adverse Events (AEs) by System Organ Class and Severity and Treatment Assignment Sorted by Decreasing Frequency

System Organ Class/ Severity	Total (N=XXXX) n (%)		A (N=XXXX) n (%)		B (N=XXXX) n (%)		C (N=XXXX) n (%)	
	n	(%)	n	(%)	n	(%)	n	(%)
Participants with one or more AEs								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Infections and infestations								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Gastrointestinal disorders								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
General disorders and administration Country conditions								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Moderate and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Severe and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Life Threatening and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Fatal	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)
Respiratory, thoracic and mediastinal disorders								
Mild and Greater	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)	xxx	(xx.x%)

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 10. Grade 3-5 Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment, Sorted by Decreasing Frequency

	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Poisoning and toxicity				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Abdominal and gastrointestinal disorders				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Streptococcal Infections				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Pain and discomfort NEC				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Viral infections NEC				
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100. AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 11. Adverse Events (AEs) by High Level Term and Severity and Treatment Assignment, Sorted by Decreasing Frequency

	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Poisoning and Toxicity				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Streptococcal Infections				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Life Threatening and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Fatal	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Allergies to foods, food additives, drugs and other chemicals				
Mild and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Moderate and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Severe and Greater	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 12. Adverse Events (AEs) Related to Study Product by High Level Term and Treatment Assignment

High Level Term/Relationship	Total (N=XXXX) n (%)	A (N=XXXX) n (%)	B (N=XXXX) n (%)	C (N=XXXX) n (%)
Participants with one or more AEs				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Viral Infections NEC				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Gastrointestinal disorders				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Poisoning and Toxicity				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Allergies to foods, food additives, drugs and other chemicals				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Mineral and Electrolyte Analyses				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Bronchitis				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Upper respiratory tract infection				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Leukocytoses NEC				
Related	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
.				
.				

N's are the number of participants enrolled.

n's are the number of participants reporting one or more AEs within a specific system organ class.

Incidence is calculated by n divided by the number enrolled x 100.

AE records included in the table have been coded into MedDRA codes by SCHARP clinical staff.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 13A. Distribution of Safety Laboratory Values, by Treatment Assignment

	Total	A	B	C
ALT				
Infusion #1 (baseline)				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Infusion #2				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
....				
Infusion #10				
N	xxx	xxx	xxx	xxx
Median (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Min, Max	xxx, xxx	xxx, xxx	xxx, xxx	xxx, xxx
Median change from baseline (IQR)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)	xxx (xxx – xxx)
Hemoglobin				
.				
.				
.				

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 13B. Safety Laboratory Values Meeting Grade 1 AE Criteria or Above, by Treatment Assignment

	Total	A	B	C
ALT				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
...	...	...	...	...
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Hemoglobin				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	...	...	...	...
...	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Platelets				
Infusion #1	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Infusion #2	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
...	...	...	...	...
Infusion #10	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 6. Boxplot for ALT by Infusion Visit and Treatment Assignment

Figure 7. Boxplot for Hemoglobin by Infusion Visit and Treatment Assignment

Figure 8. Boxplot for Platelets by Infusion Visit and Treatment Assignment

Figure 9. Boxplot for WBC by Infusion Visit and Treatment Assignment

Figure 10. Boxplot for Neutrophil Count by Infusion Visit and Treatment Assignment

Figure 11. Boxplot for Lymphocyte Count by Infusion Visit and Treatment Assignment

Figure 12. Boxplot for Creatinine by Infusion Visit and Treatment Assignment

Graphical presentation of Safety Lab distributions by infusion visit and treatment assignment.

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 13. Confirmation/Adjudication Process for HIV Infections

The process of adjudicating HIV infections is outlined in three testing algorithms (Routine, Recent Exposure and Redraw), starting from the time that the initial positive specimen is drawn through the time that the site is notified of a HIV infection.

HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 14. Pregnancy Listing

Trt.	Publication ID	LMP Date	Pregnancy outcome date	Date Last Inf. Prior to Outcome	Pregnancy Outcome	Time from Prior Inf. To LMP	# Inf. Prior to LMP	#Inf. Prior to Outcome	Total # Inf.	Comments
A	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
B	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
C	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	
	XXX-XXXX	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	dd- MMM- yyyy	text	text	X	XX	

HVTN_{xxx}/HPTN_{xxx}:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 15. HIV Adjudication Timeline

[illegible]

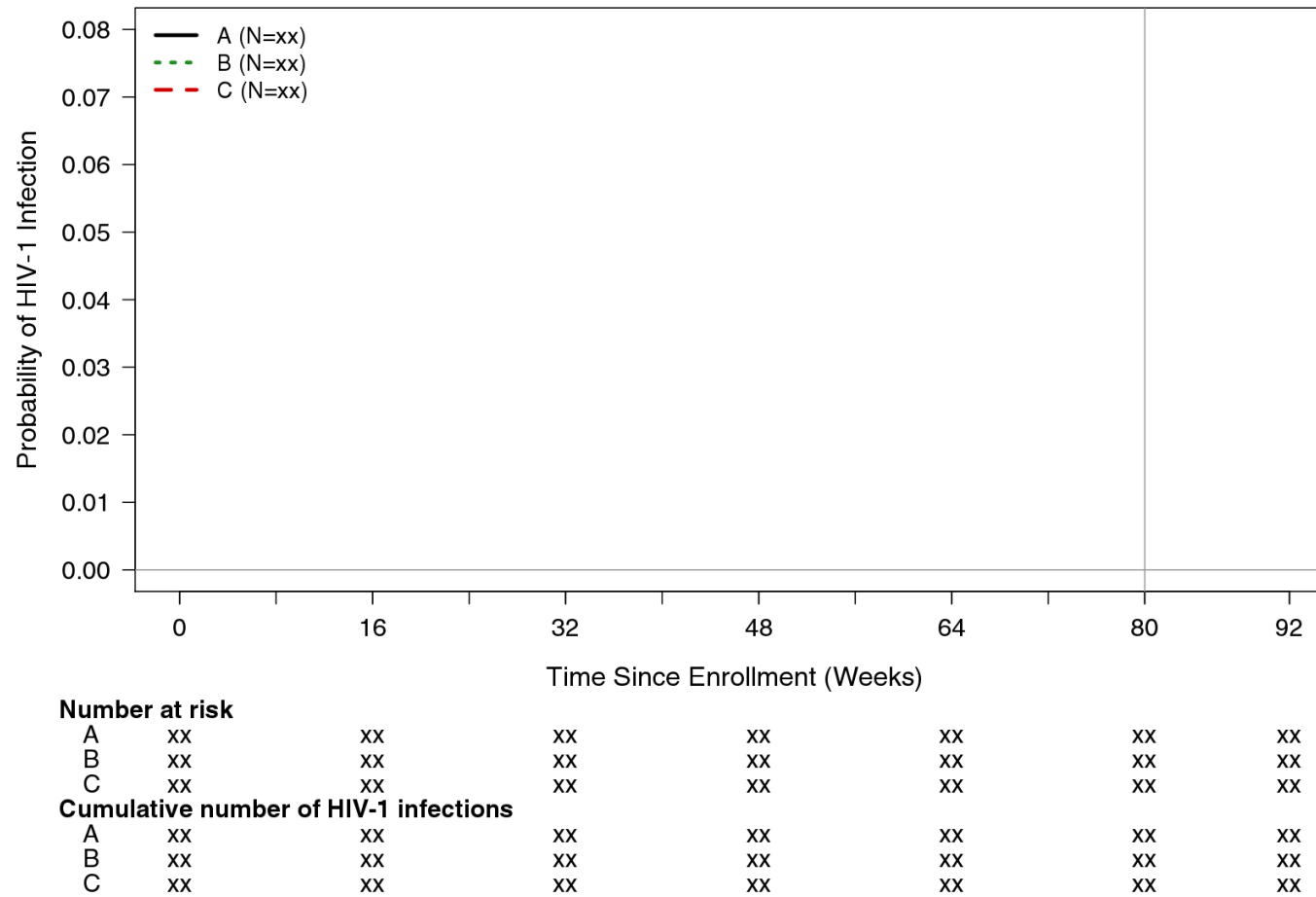
HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 16. HIV Infections

Infection Classification ¹	Trt Group	Publication ID	Initial Positive Sample Draw Date	Initial Positive Sample Draw Visit Number	Initial Positive Sample Draw Study Week	Initial Positive Sample Draw Study Day	Confirmatory Sample Draw	Enrollment Sample RNA Positive	Number of Infusions Received
Pre-Trial	A	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	B	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	C	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
MITT	A	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	B	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx
	C	xxx-xxxx xxx-xxxx	dd-MMM-yyyy dd-MMM-yyyy	xxx xxx	xxx xxx	xxx xxx	dd-MMM-yyyy dd-MMM-yyyy	text text	xxx xxx

¹Infections are categorized as either ‘Pre-Trial’ or ‘MITT’. Infections are ‘Pre-Trial’ if the enrollment sample tested HIV-positive. Pre-Trial infections will be excluded from analysis of the study endpoint as indicated in the protocol.

Data Cutoff date:[Date].



HVTNxxx/HPTNxxx:
Closed DSMB Report for DSMB meeting on [Date].
Data Cutoff date:[Date].

Table 17. ART initiation information for HIV infections

Infection Classification ¹	Trt Group	Publication ID	Post-dx ART initiation week	Excluded from primary analysis	Reason for ART initiation
Pre-Trial	A	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	B	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	C	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
MITT	A	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	B	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text
	C	xxx-xxxx	dd-MMM-yyyy	text	text
		xxx-xxxx	dd-MMM-yyyy	text	text

¹Infections are categorized as either ‘Pre-Trial’ or ‘MITT’. Infections are ‘Pre-Trial’ if the enrollment sample tested HIV-positive. Pre-Trial infections will be excluded from analysis of the study endpoint as indicated in the protocol.

HVTNxxx/HPTNxxx:

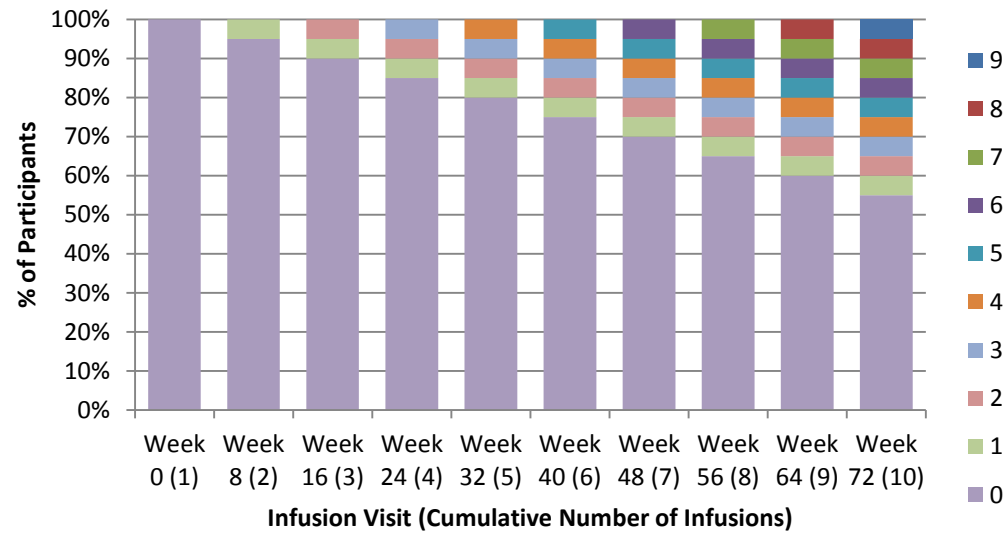
Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 15. Viral Load Over Time Among All Infected MITT Participants

Longitudinal pre-ART viral load measurements are presented by treatment group for MITT infected participants. Individual participant trajectories are indicated by solid black lines, while mean pre-ART viral load measures within a treatment group are plotted using a dashed red line. Means are only estimated for weeks with at least three participants with pre-ART viral load data.

Data Cutoff date:[Date].

[illegible]

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 18a. Visit Retention for All MITT HIV-1 Infected Participants by Treatment Assignment

	Total	A	B	C
Participants Enrolled In Schedule 2	xxx	xxx	xxx	xxx
Week 2 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 4 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)				
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 6 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)				
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
.				
.				
Week 24 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Table 18b. Visit Retention for All Pre-Trial HIV-1 Infected Participants and All HIV-2 Infected Participants by Treatment Assignment

	Total	A	B	C
Participants Enrolled In Schedule 3	xxx	xxx	xxx	xxx
Week 2 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 4 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window or did not receive prev. infusion)				
Expected (in visit window and received previous infusion)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Attended visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Missed visit	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not yet attended (still in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Week 24 Post Diagnosis				
Terminated	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Not Expected (not in window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Expected (in visit window)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

HVTNxxx/HPTNxxx:

Closed DSMB Report for DSMB meeting on [Date].

Data Cutoff date:[Date].

Figure 17. Cumulative Enrollment

Line plot of the observed and expected accrual for all sites combined.

Appendix B

The CASI behavioral risk survey administered at the enrollment visit in HVTN 704/HPTN 085 and at South African sites in HVTN 703/HPTN 081 is included below. The survey is used for constructing baseline covariates potentially predictive of the primary endpoint considered for inclusion in the superlearner HIV-1 risk predictor described in Section 8.6.

AMP Study

0%

Collection: LOGIN
Contains: PTID, SCHEDULE, VISIT, VISITCHK

AMP Study

Question: PTID
Required



Site Staff: Please answer the following questions. Please enter a valid Participant ID in the following format: 111-1-1111-1

Question: SCHEDULE
Required

Scale Summary		
Code	Label	Show-If
1	Schedule 1	
2	Schedule 2 (HIV Infected)	
3	Schedule 3 (HIV Infected at Enrollment)	
4	Schedule 4	



Which study Schedule is the participant currently in?

- ☐ Schedule 1
- ☐ Schedule 2 (HIV Infected)
- ☐ Schedule 3 (HIV Infected at Enrollment)
- ☐ Schedule 4

Question: VISIT
Required

Scale Summary		
Code	Label	Show-If
02.0	Visit 02.0 (Enrollment/Infusion #1)	
04.0	Visit 04.0 (Infusion #2)	
07.0	Visit 07.0 (Infusion #3)	
09.0	Visit 09.0 (Infusion #4)	
11.0	Visit 11.0 (Infusion #5)	
13.0	Visit 13.0 (Infusion #6)	
15.0	Visit 15.0 (Infusion #7)	
17.0	Visit 17.0 (Infusion #8)	
19.0	Visit 19.0 (Infusion #9)	
21.0	Visit 21.0 (Infusion #10)	
26.0	Visit 26.0 (End Visit)	

35.0	Visit 35.0	
48.0	Visit 48.0	
72.0	Visit 72.0	
74.0	Visit 74.0	
76.0	Visit 76.0	
78.0	Visit 78.0	



▶ What is the visit code for this visit?

Please select the visit code from the drop down menu.

Question: VISITCHK
Required



▶ Please confirm the visit code by entering it here:

Please enter a "0" first if the visit is before 10.0 - for example, "07.0"

Auto Page Break

Click “next” to select the appropriate language.

Page Break

Question: LANG_SELECT
Required

Scale Summary		
Code	Label	Show-If
1033	English	
1077	Zulu	(Error!)
1076	Xhosa	(Error!)
1132	Sotho	(Error!)
1074	Setswana	<i>Never Shown</i>
1078	Shona	<i>Never Shown</i>
1073	Dholuo	(Error!)
1116	Chichewa	<i>Never Shown</i>
1046	Portuguese	<i>Never Shown</i>
1089	Swahili	<i>Never Shown</i>
1115	Sepedi	(Error!)



1. Language choice

- ☐ English
- ☐ Zulu
- ☐ Xhosa
- ☐ Sotho
- ☐ Setswana
- ☐ Shona
- ☐ Dholuo
- ☐ Chichewa
- ☐ Portuguese
- ☐ Swahili
- ☐ Sepedi

Page Break

Collection: STAFF_QUESTIONS
Contains: COMPLETEDBY

Question: COMPLETEDBY
Required

Scale Summary		
Code	Label	Show-If
1	Participant is completing questionnaire	
2	Interviewer is administering questionnaire	



2. Is this questionnaire being completed by the participant directly or is an interviewer from the site staff reading the questionnaire to the participant and entering participant's responses?

- ☐ Participant is completing questionnaire
- ☐ Interviewer is administering questionnaire

Page Break

Collection: TOTAL_NUM_PARTNERS

Contains: VAS, SEX_BEHAVIOR, VAGINA, RECEP_VAGINAL, RECEP_ANAL, PENIS, IVAS, IVASW, INSERTIVE_VAGINAL, IVASM, INS_ANAL, MSP

Many people are taking part in this research study. We ask the same questions of all participants. However, some questions may not apply to you.

Please answer these questions honestly. We make no judgments about how you have sex or the number of times or with whom. We do not judge about alcohol or drug use.

Your answers to these questions will help us understand the type of behaviors our participants are doing while in this study.

Page Break

The first set of questions is about your sexual relationships with men, women, and transgender people in the last months. By men we mean persons who were considered male at birth and currently identify as male. By women we mean persons who were considered female at birth and currently identify as female. By transgender we mean persons whose gender identity or expression differs from their biological sex assigned at birth.

A transgender woman is a person who is considered male at birth and who now identifies primarily as female. A transgender woman may have a vagina and/or penis. A transgender man is a person who is considered female at birth and who now identifies primarily as male. A transgender man may have a penis and/or a vagina.

By sex, we are talking about VAGINAL sex (when a penis is put into the vagina) or ANAL sex (when a penis is put into the anus or butt). For some questions, we will be asking about sex without a condom. By this we mean that a condom was not used the whole time the penis was inserted, or the condom broke, tore, spilled or slipped off. A condom can be either a male or female condom.

Page Break

Question: VAS
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



3. In the last months, how many people did you have vaginal or anal sex with (with or without a condom)?

- ☐ people
- ☐ Prefer not to answer

Auto Page Break

Jump-To: JMP1

Description:

Jump-To-Item: PPT_RISK_BEHAVIOR

Jump-If: (VAS.TEXT = 0) or (VAS = 99:[Prefer not to answer])

Collection: SEX_BEHAVIOR

Contains: VS, AS, VASC, VAS7, VASC7

Show if: (VAS.TEXT >= 1)

Question: VS

Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



4. Of these people, how many did you have vaginal sex with (with or without a condom) in the last months?

- ☐ people
- ☐ Prefer not to answer

Question: AS

Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



5. Of these people, how many did you have anal sex with (with or without a condom) in the last months?

- ☐ people
- ☐ Prefer not to answer

Question: VASC

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	



6. In general, in the last months, how often did you use a condom during vaginal or anal sex?

- ☐ Never
- ☐ Sometimes
- ☐ Always
- ☐ Prefer not to answer

Page Break

Question: VAS7

Required

Show if: (VAS ≠ 99:[Prefer not to answer]) and (VAS.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



7. In **the last 7 days**, how many times have you had vaginal or anal sex (with or without a condom)?

- ☐ # of times
- ☐ Prefer not to answer

Auto Page Break

Question: VASC7

Required

Show if: (VAS7 ≠ 99:[Prefer not to answer]) and (VAS7.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	



8. In general, in **the last 7 days**, how often did you use a condom during vaginal or anal sex?

- ☐ Never
- ☐ Sometimes
- ☐ Always
- ☐ Prefer not to answer

Page Break

Question: VAGINA
Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



9. Do you have a vagina?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Collection: RECEP_VAGINAL

Contains: VSM, VSMNC, VSTW, VSTWNC, VSTM, VSTMNC

Show if: (VS.TEXT > 0) and (VAGINA = 1:[Yes])

The next set of questions ask about the people you have had RECEPTIVE vaginal sex with in the last months. By receptive vaginal sex, we mean when a penis is put into your vagina

Page Break

Question: VSM
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer to not answer	



10. In the last months, how many men did you have vaginal sex with (with or without a condom)? (By men, we mean persons who are considered male at birth and currently identify as male.)

- ☐ # of men
- ☐ Prefer to not answer

Auto Page Break

Question: VSMNC

Required

Show if: (VSM.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1		
2	Prefer not to answer	



11. With how many **men** did you have **vaginal sex** without a condom?

- ☐ # of men
- ☐ Prefer not to answer

Page Break

Question: VSTW
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



12. In the last months, how many **transgender women** did you have vaginal sex with (with or without a condom)? (By **transgender women**, we mean persons who are considered male at birth and now identify primarily as female.)

- ☐ # of transgender women
- ☐ Prefer not to answer

Auto Page Break

Question: VSTWNC
Required
Show if: (VSTW.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



13. With how many **transgender women** did you have **vaginal sex** without a condom?

- ☐ # of transgender women
- ☐ Prefer not to answer

Page Break

Question: VSTM
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



14. In the last months, how many **transgender men** did you have vaginal sex with (with or without a condom)? (By **transgender men**, we mean persons who are considered female at birth and now identify primarily as male.)

- ☐ # of transgender men
- ☐ Prefer not to answer

Auto Page Break

Question: VSTMNC

Required

Show if: (VSTM.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



15. With how many **transgender men** did you have **vaginal sex** without a condom?

- ☐ # of transgender men
- ☐ Prefer not to answer

Page Break

Collection: RECEP_ANAL
Contains: RASM, RASMNC, RASTW, RASTWNC, RASTM, RASTMNC
Show if: (AS.TEXT > 0)

The next set of questions asks about the people you have had RECEPTIVE anal sex with in the last months. By receptive anal sex, we mean when a penis is put into your anus or butt.

Page Break

Question: RASM
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



16. In the last months, how many **men** did you have **receptive anal sex** with (with or without a condom)? (By **men**, we mean persons who are considered male at birth and currently identify as male.)

- ☐ # of men
- ☐ Prefer not to answer

Auto Page Break

Question: RASMNC

Required

Show if: (RASM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



17. With how many **men** did you have **receptive anal sex** without a condom?

- ☐ # of men
- ☐ Prefer not to answer

Page Break

Question: RASTW
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



18. In the last months, how many **transgender women** did you have **receptive anal sex** with (with or without a condom)? (By **transgender women**, we mean persons who are considered male at birth and now identify primarily as female.)

- ☐ # of transgender women
- ☐ Prefer not to answer

Auto Page Break

Question: RASTWNC

Required

Show if: (RASTW.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



19. With how many **transgender women** did you have **receptive anal sex** without a condom?

- ☐ # of transgender women
- ☐ Prefer not to answer

Page Break

Question: RASTM
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



20. In the last months, how many **transgender men** did you have **receptive anal sex** with (with or without a condom)? (By **transgender men**, we mean persons who are considered female at birth and now identify primarily as male.)

- ☐ # of transgender men
- ☐ Prefer not to answer

Auto Page Break

Question: RASTMNC

Required

Show if: (RASTM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

- 

21. With how many **transgender men** did you have **receptive anal sex** without a condom?

☐ # of transgender men

☐ Prefer not to answer

Page Break

Question: PENIS
Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



22. Do you have a penis?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

The next set of questions ask you about the people you have **vaginal and/or anal INSERTIVE** sex with. By insertive sex, we mean that **you** put **your** penis into someone else's vagina, anus, or butt.

Page Break

Question: IVAS

Required

Show if: (PENIS = 1:[Yes]) and (VAS.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



23. In the last months, how many people did you have **insertive vaginal or anal sex** with (with or without a condom)?

☐ # of people

☐ Prefer not to answer

Page Break

Question: IVASW

Required

Show if: (IVAS.TEXT >= 1) and (PENIS = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



24. How many of these people were **women**? (By women, we mean persons who are considered female at birth and currently identify as female.)

- ☐ # of women
- ☐ Prefer not to answer

Auto Page Break

Collection: INSERTIVE_VAGINAL
Contains: IVSW, IVSWNC
Show if: (IVASW.TEXT >= 1) and (PENIS = 1:[Yes])

Question: IVSW

Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



25. Of these **women**, how many did you have **insertive vaginal sex** with (with or without a condom)?

- ☐ # of women
- ☐ Prefer not to answer

Auto Page Break

Question: IVSWNC

Required

Show if: (IVSW.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

- 

26. With how many of these **women** did you have **insertive vaginal sex** without a condom?

☐ # of women

☐ Prefer not to answer

Page Break

Question: IVASM
Required
Show if: (IVAS.TEXT >= 1) and (PENIS = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

-  27. How many of these people were **men**? (By men, we mean persons who are considered male at birth and currently identify as male.)
- ☐ # of men
- ☐ Prefer not to answer

Collection: INS_ANAL
Contains: IASM, IASMNC, IVASTW, IASTW, IASTWNC, IVASTM, IASTM, IASTMNC
Show if: (AS.TEXT > 0) and (PENIS = 1:[Yes])

Question: IASM
Required
Show if: (AS ≠ 99:[Prefer not to answer]) and (AS.TEXT > 0) and (IVASM ≠ 99:[Prefer not to answer]) and (IVASM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

-  28. Of these **men**, how many did you have **insertive anal sex** with (with or without a condom)?
- ☐ # of men
- ☐ Prefer not to answer

Auto Page Break

Question: IASMNC

Required

Show if: (IASM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



29. With how many of these **men** did you have **insertive anal sex** without a condom?

- ☐ # of men
- ☐ Prefer not to answer

Page Break

Question: IVASTW

Required

Show if: (IVAS ≠ 99:[Prefer not to answer]) and (IVAS.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



30. How many of these people were **transgender women**? (By transgender women, we mean persons who are considered male at birth and now identify primarily as female.)

- ☐ # of transgender women
- ☐ Prefer not to answer

Question: IASTW

Required

Show if: (AS.TEXT > 0) and (IVASTW.TEXT > 0) and (IVASTW ≠ 99:[Prefer not to answer]) and (AS ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



31. Of these **transgender women**, how many did you have **insertive anal sex** with (with or without a condom)?

- ☐ # of transgender women
- ☐ Prefer not to answer

Auto Page Break

Question: IASTWNC

Required

Show if: (IASTW.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



32. With how many of these **transgender women** did you have **insertive anal sex** without a condom?

- ☐ # of transgender women
- ☐ Prefer not to answer

Page Break

Question: IVASTM

Required

Show if: (IVAS $\neq$ 99:[Prefer not to answer]) and (IVAS.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



33. How many of these people were **transgender men**? (By transgender men, we mean persons who are considered female at birth and now identify primarily as male.)

- ☐ # of transgender men
- ☐ Prefer not to answer

Question: IASTM

Required

Show if: (AS $\neq$ 99:[Prefer not to answer]) and (AS.TEXT > 0) and (IVASTM $\neq$ 99:[Prefer not to answer]) and (IVASTM $\neq$ 99:[Prefer not to answer]) and (IVASTM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



34. Of these **transgender men**, how many did you have **insertive anal sex** with (with or without a condom)?

- ☐ # of transgender men
- ☐ Prefer not to answer

Auto Page Break

Question: IASTMNC

Required

Show if: (IASTM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



35. With how many of these **transgender men** did you have **insertive anal sex** without a condom?

- ☐ # of transgender men
- ☐ Prefer not to answer

Page Break

The next set of questions ask about your main partner. By main partner, we mean someone who you lived with or saw a lot, or to whom you felt a special emotional commitment, and with whom you had vaginal or anal sex.

Page Break

Question: MSP

Required

Show if: (VAS.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



36. Of the persons who you had **vaginal or anal sex** with, is/are any of them your main sexual partner(s)?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Collection: MAIN_PARTNERS

Contains: MSPCH, MSPNUM, MSPC, MSPID, MSPO, MSPEX, MSPHIV, MSPDR, MSPSTD, MSPWORRIED, OSP

Show if: (MSP = 1:[Yes])

Question: MSPCH

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



37. Have you changed your main sex partner in the last months?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Auto Page Break

Question: MSPNUM

Required

Show if: (MSPCH = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	



38. How many main sex partners have you had in the last months?

- ☐ # of main sex partners
- ☐ Prefer not to answer

Page Break

Question: MSPC

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	



39. How often did you use condoms when you had vaginal or anal sex with your main partner(s) in the last months?

- ☐ Never
- ☐ Sometimes
- ☐ Always
- ☐ Prefer not to answer

Page Break

Question: MSPID

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



40. Do any of your main partner(s) inject drugs to get high?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPO

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



41. Have any of your main partner(s) had sex with someone else besides you during the same time period?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Auto Page Break

Question: MSPEX

Required

Show if: (MSPO = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



42. Did any of your main partner(s) have vaginal or anal sex with another person in exchange for money, drugs, goods, or services?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Page Break

Question: MSPHIV

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



43. Are any of your main partner(s) HIV-infected?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPDR

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



44. Were any of your main partner(s) ever drunk or high on drugs while you were having sex with them?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPSTD

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



45. Have any of your main partner(s) been diagnosed with or treated for a sexually transmitted infection the last months?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Page Break

Question: MSPWORRIED

Required

Show if: (MSPHIV = 2:[No]) or (MSPHIV = 3:[Don't know])

Scale Summary		
Code	Label	Show-If
1	Very worried	
2	Somewhat worried	
3	Not at all worried	
99	Prefer not to answer	



46. How worried are you that your main partner(s) may become infected with HIV in **the next year?**

- ☐ Very worried
- ☐ Somewhat worried
- ☐ Not at all worried
- ☐ Prefer not to answer

Page Break

Question: OSP**Required****Show if:** (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



47. Are there any other people, not including your main partner(s), that you recently had sex with?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Collection: OTHER_PARTNERS

Contains: OSPID, OSPSO, OSPEX, OSPHIV, OSPHIVNC, OSPDR, OSPSTD, OSPWORRIED

Show if: (OSP = 1:[Yes])

The next set of questions ask you about the other people you have had sex with recently.

Question: OSPID

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



48. During the last months, did you have vaginal or anal sex with someone who injected drugs to get high?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPSO

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



49. During the last months, did you have vaginal or anal sex with someone who was having sex with someone else besides you during the same time period?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Auto Page Break

Question: OSPEX

Required

Show if: (OSPSO = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



50. Did any of these persons have vaginal or anal sex with another person in exchange for money, drugs, goods, or services?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Page Break

Question: OSPHIV

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



51. During the last months, did you have vaginal or anal sex with someone who was HIV-infected?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Auto Page Break

Question: OSPHIVNC

Required

Show if: (OSPHIV = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



52. Did you have **vaginal or anal sex** without a condom with any HIV-infected persons?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Page Break

Question: OSPDR

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



53. During the last months, did you have vaginal or anal sex with someone who was drunk or high on drugs while you were having sex with them?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Page Break

Question: OSPSTD

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	



54. During the last months, did you have vaginal or anal sex with someone who has recently been diagnosed with, or treated for one or more sexually transmitted infections?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPWORRIED

Required

Show if: (OSPHIV = 2:[No]) or (OSPHIV = 3:[Don't know])

Scale Summary		
Code	Label	Show-If
1	Very worried	
2	Somewhat worried	
3	Not at all worried	
99	Prefer not to answer	



55. How worried are you that one or more of your sex partners may become infected with HIV in **the next year**?

- ☐ Very worried
- ☐ Somewhat worried
- ☐ Not at all worried
- ☐ Prefer not to answer

Page Break

Collection: PPT_RISK_BEHAVIOR

Contains: ALCOH, ALCOHNUM, ALCOHB, VASDRUNK, IDUSE, IDNEEDLESHARE, MDKS, MS2HR, CRCO, CRCOS2HR, PRCO, PRCOS2HR, AMPMETH, AMPMETS2HR, METMAN, METMANS2HR, HERMED, HERMEDS2HR, MDMA, MDMAS2HR, WHO, WHOS2HR, POP, POPS2HR, OTHDRUG, OTHDRUG_FREQ, OTHDRUGS2HR, CIGVAPE, VASEX, HIVINFYR

The next set of questions ask about some other behaviors.

Question: ALCOH

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Monthly or less	
3	2-4 times a month	
4	2-3 times a week	
5	4 or more times a week	
99	Prefer not to answer	



56. During the last months, how often did you have a drink containing alcohol?

- ☐ Never
- ☐ Monthly or less
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week
- ☐ Prefer not to answer

Auto Page Break

Question: ALCOHNUM

Required

Show if: (ALCOH ≠ 1:[Never]) and (ALCOH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	1 or 2	
2	3 or 4	
3	5 or 6	
4	7 to 9	
5	10 or more	
99	Prefer not to answer	



57. During the last months, on a typical day when you were drinking, how many standard drinks containing alcohol did you have?

- ☐ 1 or 2
- ☐ 3 or 4
- ☐ 5 or 6
- ☐ 7 to 9
- ☐ 10 or more
- ☐ Prefer not to answer

Question: ALCOHB

Required

Show if: (ALCOH ≠ 1:[Never]) and (ALCOH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Never	
2	Less than monthly	
3	Monthly	
4	Weekly	
5	Daily or almost daily	
99	Prefer not to answer	



58. During the last months, how often did you have 6 or more drinks on one occasion?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily
- ☐ Prefer not to answer

Question: VASDRUNK

Required

Show if: (VAS ≠ 99:[Prefer not to answer]) and (VAS.TEXT ≠ 0) and (ALCOH ≠ 99:[Prefer not to answer]) and (ALCOH ≠ 1:[Never])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



59. During the last months, did you have vaginal or anal sex while you were drunk?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: IDUSE
Required**Scale Summary**

Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



60. During the last months, did you inject any drugs to get high?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Auto Page Break

Question: IDNEEDLESHARE
Required
Show if: (IDUSE = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



61. Did you share a needle with others?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

**Question: MDKS
Required**

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



62. During the last months, how often did you use Marijuana, dagga, K2, spice?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: MS2HR

Required

Show if: (VAS.TEXT > 0) and (MDKS ≠ 1:[Never]) and (MDKS ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



63. During the last months, did you have vaginal or anal sex within 2 hours of you using marijuana?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: CRCO
Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



64. During the last months, how often did you use crack cocaine?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: CRCOS2HR

Required

Show if: (VAS.TEXT > 0) and (CRCO ≠ 1:[Never]) and (CRCO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



65. During the last months, did you have vaginal or anal sex within 2 hours of you using crack cocaine?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: PRCO
Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



66. During the last months, how often did you use powder cocaine?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: PRCOS2HR

Required

Show if: (VAS.TEXT > 0) and (PRCO ≠ 1:[Never]) and (PRCO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



67. During the last months, did you have vaginal or anal sex within 2 hours of you using powder cocaine?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

**Question: AMPMETH
Required**

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



68. During the last months, how often did you use amphetamine/methamphetamine, crystal meth, Khat/Cat, or tik?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: AMPMETS2HR

Required

Show if: (VAS.TEXT > 0) and (AMPMETH ≠ 1:[Never]) and (AMPMETH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



69. During the last months, did you have vaginal or anal sex within 2 hours of you using amphetamine/methamphetamine, crystal meth, Khat/Cat, or tik?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

**Question: METMAN
Required**

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



70. During the last months, how often did you use methaqualone or mandrax?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: METMANS2HR

Required

Show if: (VAS.TEXT > 0) and (METMAN ≠ 1:[Never]) and (METMAN ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



71. During the last months, did you have vaginal or anal sex within 2 hours of you using methaqualone or mandrax?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: HERMED
Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



72. During the last months, how often did you use heroin, prescription pain killers/medications?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: HERMEDS2HR

Required

Show if: (VAS.TEXT > 0) and (HERMED ≠ 1:[Never]) and (HERMED ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

- 

73. During the last months, did you have vaginal or anal sex within 2 hours of you using heroin, prescription pain killers/medications?

☐ Yes
 ☐ No
 ☐ Prefer not to answer

Page Break

Question: MDMA
Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



74. During the last months, how often did you use MDMA or Ecstasy?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: MDMAS2HR

Required

Show if: (VAS.TEXT > 0) and (MDMA ≠ 1:[Never]) and (MDMA ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



75. During the last months, did you have vaginal or anal sex within 2 hours of you using MDMA or Ecstasy?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

**Question: WHO
Required**

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



76. During the last months, how often did you use whoonga/wunga or nyaope?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: WHOS2HR

Required

Show if: (VAS.TEXT > 0) and (WHO ≠ 1:[Never]) and (WHO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



77. During the last months, did you have vaginal or anal sex within 2 hours of you using Whoonga/wunga or nyaope?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

**Question: POP
Required**

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



78. During the last months, how often did you use poppers?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: POPS2HR**Required****Show if:** (VAS.TEXT > 0) and (POP ≠ 1:[Never]) and (POP ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



79. During the last months, did you have vaginal or anal sex within 2 hours of you using Poppers?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: OTHDRUG
Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	Not applicable - No other drugs used	
99	Prefer not to answer	



80. During the last months, have you used any other drugs? If yes, please specify.

- ☐ Yes
- ☐ Not applicable - No other drugs used
- ☐ Prefer not to answer

Page Break

Question: OTHDRUG_FREQ

Required

Show if: (OTHDRUG = 1:[Yes])

Scale Summary		
Code	Label	Show-If
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	



81. During the last months, how often did you use ?

- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Page Break

Question: OTHDRUGS2HR

Required

Show if: (VAS.TEXT > 0) and (OTHDRUG_FREQ ≠ 99:[Prefer not to answer]) and (OTHDRUG_FREQ was-answered)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



82. During the last months, did you have vaginal or anal sex within 2 hours of you using ?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: CIGVAPE
Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



83. Do you currently smoke cigarettes or e-cigs (Vape)?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Page Break

Question: VASEX

Required

Show if: (VAS.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



84. In the last months, have you given and/or received money, gifts, drugs, goods, shelter, or services in exchange for vaginal or anal sex?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: HIVINFYR

Required

Show if: (SCHEDULE = 1:[Schedule 1]) or (SCHEDULE = 4:[Schedule 4])

Scale Summary		
Code	Label	Show-If
1	Not at all likely	
2	Somewhat unlikely	
3	Neutral/No opinion	
4	Somewhat likely	
5	Extremely Likely	
99	Prefer not to answer	



85. How likely do you think it is that you may become infected with HIV in **the next year**?

- ☐ Not at all likely
- ☐ Somewhat unlikely
- ☐ Neutral/No opinion
- ☐ Somewhat likely
- ☐ Extremely Likely
- ☐ Prefer not to answer

Collection: STUDY_PRODUCT

Contains: ANTIPLAC, HIGHLOW, INVINFUSION

Show if: (SCHEDULE = 1:[Schedule 1]) or (SCHEDULE = 4:[Schedule 4])

Question: ANTIPLAC

Required

Show if: (VISIT is-any-of 09.0:[Visit 09.0 (Infusion #4)] or 15.0:[Visit 15.0 (Infusion #7)] or 21.0:[Visit 21.0 (Infusion #10)] or 26.0:[Visit 26.0 (End Visit)] or 72.0:[Visit 72.0] or 74.0:[Visit 74.0] or 76.0:[Visit 76.0] or 78.0:[Visit 78.0])

Scale Summary		
Code	Label	Show-If
1	VRC01	
2	Placebo	
3	Don't know	
99	Prefer not to answer	



86. Do you think you received the VRC01 antibody or placebo in this study?

- ☐ VRC01
- ☐ Placebo
- ☐ Don't know
- ☐ Prefer not to answer

Auto Page Break

Question: HIGHLOW

Required

Show if: (ANTIPLAC = 1:[VRC01])

Scale Summary		
Code	Label	Show-If
1	High Dose	
2	Low Dose	
3	Unsure	
99	Prefer not to answer	



87. Do you think you received the high dose, low dose, or are you unsure?

- ☐ High Dose
- ☐ Low Dose
- ☐ Unsure
- ☐ Prefer not to answer

Question: INVINFUSION

Required

Show if: (VISIT = 02.0:[Visit 02.0 (Enrollment/Infusion #1)])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	



88. Have you, a family member, or close friend ever had an IV infusion?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Powered by DatStat

Appendix C

The abbreviated CASI behavioral risk survey administered at the enrollment visit at sites outside of South Africa in HVTN 703/HPTN 081 is included below. The survey is used for constructing baseline covariates potentially predictive of the primary endpoint considered for inclusion in the superlearner HIV-1 risk predictor described in Section 8.6.

AMP Study

0%

Collection: LOGIN
Contains: PTID, SCHEDULE, VISIT, VISITCHK

AMP Study

Question: PTID
Required

Site Staff: Please answer the following questions. Please enter a valid Participant ID in the following format: 111-1-1111-1

Question: SCHEDULE
Required

Scale Summary		
Code	Label	Show-If
1	Schedule 1	
2	Schedule 2 (HIV Infected)	
3	Schedule 3 (HIV Infected at Enrollment)	
4	Schedule 4	

Which study Schedule is the participant currently in?

- ☐ Schedule 1
- ☐ Schedule 2 (HIV Infected)
- ☐ Schedule 3 (HIV Infected at Enrollment)
- ☐ Schedule 4

Question: VISIT
Required

Scale Summary		
Code	Label	Show-If
02.0	Visit 02.0 (Enrollment/Infusion #1)	
04.0	Visit 04.0 (Infusion #2)	
07.0	Visit 07.0 (Infusion #3)	
09.0	Visit 09.0 (Infusion #4)	
11.0	Visit 11.0 (Infusion #5)	
13.0	Visit 13.0 (Infusion #6)	
15.0	Visit 15.0 (Infusion #7)	
17.0	Visit 17.0 (Infusion #8)	
19.0	Visit 19.0 (Infusion #9)	
21.0	Visit 21.0 (Infusion #10)	
26.0	Visit 26.0 (End Visit)	

35.0	Visit 35.0	
48.0	Visit 48.0	
72.0	Visit 72.0	
74.0	Visit 74.0	
76.0	Visit 76.0	
78.0	Visit 78.0	

▶ What is the visit code for this visit?

Please select the visit code from the drop down menu.

Question: VISITCHK
Required

▶ Please confirm the visit code by entering it here:

Please enter a "0" first if the visit is before 10.0 - for example, "07.0"

Click "next" to select the appropriate language.

Question: LANG_SELECT
Required

Scale Summary		
Code	Label	Show-If
1033	English	
1077	Zulu	<i>Never Shown</i>
1076	Xhosa	<i>Never Shown</i>
1132	Sotho	<i>Never Shown</i>
1074	Setswana	(Error!)
1078	Shona	(Error!)
1073	Dholuo	<i>Never Shown</i>
1116	Chichewa	<i>Never Shown</i>
1046	Portuguese	<i>Never Shown</i>
1089	Swahili	(Error!)

1. Language choice

- ☐ English
- ☐ Zulu
- ☐ Xhosa
- ☐ Sotho
- ☐ Setswana
- ☐ Shona
- ☐ Dholuo
- ☐ Chichewa
- ☐ Portuguese
- ☐ Swahili

Collection: STAFF_QUESTIONS
Contains: COMPLETEDBY

Question: COMPLETEDBY
Required

Scale Summary		
Code	Label	Show-If

1	Participant is completing questionnaire	
2	Interviewer is administering questionnaire	

2. Is this questionnaire being completed by the participant directly or is an interviewer from the site staff reading the questionnaire to the participant and entering participant's responses?

- ☐ Participant is completing questionnaire
- ☐ Interviewer is administering questionnaire

Collection: TOTAL_NUM_PARTNERS

Contains: SEXNUM, NCNUM, SEX_BEHAVIOR, MSP

Many people are taking part in this research study. We ask the same questions of all participants. However, some questions may not apply to you.

Please answer these questions honestly. We make no judgments about how you have sex or the number of times or with whom. We do not judge about alcohol or drug use.

Your answers to these questions will help us understand participants' behaviors so that we may assess effectiveness of current HIV prevention methods.

The first set of questions is about your sexual relationships with men, in the last months. By men we mean persons who are considered male at birth and currently identify as male.

By sex, we are talking about VAGINAL sex (when a penis is put into the vagina). For some questions, we will be asking about sex without a condom. By this we mean that a condom was not used the whole time the penis was inserted, or the condom broke, tore, spilled or slipped off. A condom can be either a male or female condom.

Question: SEXNUM
Required

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

3. In the last months, how many men did you have vaginal sex with (with or without a condom)?

- ☐ # of men
- ☐ Prefer not to answer

Jump-To: JMP1

Description:

Jump-To-Item: PPT_RISK_BEHAVIOR

Jump-If: (SEXNUM.TEXT = 0) or (SEXNUM = 99:[Prefer not to answer])

Question: NCNUM

Required

Show if: (SEXNUM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

4. With how many men did you have vaginal sex without a condom?

- ☐ # of men
- ☐ Prefer not to answer

Collection: SEX_BEHAVIOR

Contains: CONDFREQ, SXTIMES7D, CONDFREQ7D

Show if: (SEXNUM.TEXT > 0)

Question: CONDFREQ
Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	

5. In general, in the last months, how often did you use a condom during vaginal sex?

- ☐ Never
☐ Sometimes
☐ Always
☐ Prefer not to answer

Question: SXTIMES7D
Required

Show if: (SEXNUM ≠ 99:[Prefer not to answer]) and (SEXNUM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

6. In **the last 7 days**, how many times have you had vaginal sex (with or without a condom)?

- ☐ # of times
☐ Prefer not to answer

Question: CONDFREQ7D
Required

Show if: (SXTIMES7D ≠ 99:[Prefer not to answer]) and (SXTIMES7D.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	

7. In general, in **the last 7 days**, how often did you use a condom during vaginal sex?

- ☐ Never
☐ Sometimes
☐ Always
☐ Prefer not to answer

The next set of questions asks about your main partner. By main partner, we mean someone who you lived with or saw a lot, or to whom you felt a special commitment, and with whom you had vaginal sex.

Question: MSP
Required

Show if: (SEXNUM.TEXT >= 1)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

8. Of the persons who you had vaginal sex with, is/are any of them your main sexual partner(s)?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Collection: MAIN_PARTNERS

Contains: MSPCH, MSPNUM, MSPC, MSPID, MSPO, MSPEX, MSPHIV, MSPDR, MSPSTD, MSPWORRIED, OSP

Show if: (MSP = 1:[Yes])

Question: MSPCH

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

9. Have you changed your main sex partner in the last months?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: MSPNUM

Required

Show if: (MSPCH = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1		
99	Prefer not to answer	

10. How many main sex partners have you had in the last months?

- ☐ # of main sex partners
- ☐ Prefer not to answer

Question: MSPC

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Never	
2	Sometimes	
3	Always	
99	Prefer not to answer	

11. How often did you use condoms when you had vaginal sex with your main partner(s) in the last months?

- ☐ Never
- ☐ Sometimes
- ☐ Always
- ☐ Prefer not to answer

Question: MSPID

Required

Show if: (MSP = 1:[Yes])

Scale Summary		

Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

12. Do any of your main partner(s) inject drugs to get high?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: MSPO

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

13. Have any of your main partner(s) had sex with someone else besides you during the same time period?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: MSPEX

Required

Show if: (MSPO = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

14. Did any of your main partner(s) have vaginal sex with another person in exchange for money, drugs, goods, or services?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: MSPHIV

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

15. Are any of your main partner(s) HIV-infected?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPDR

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

16. Were any of your main partner(s) ever drunk or high on drugs while you were having sex with them?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPSTD

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

17. Have any of your main partner(s) been diagnosed with or treated for a sexually transmitted infection the last months?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: MSPWORRIED

Required

Show if: (MSPHIV = 2:[No]) or (MSPHIV = 3:[Don't know])

Scale Summary		
Code	Label	Show-If
1	Very worried	
2	Somewhat worried	
3	Not at all worried	
99	Prefer not to answer	

18. How worried are you that your main partner(s) may become infected with HIV in **the next year**?

- ☐ Very worried
- ☐ Somewhat worried
- ☐ Not at all worried
- ☐ Prefer not to answer

Question: OSP

Required

Show if: (MSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

19. Are there any other people, not including your main partner(s), that you recently had sex with?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Collection: OTHER_PARTNERS

Contains: OSPID, OSPSO, OSPEX, OSPHIV, OSPHIVNC, OSPDR, OSPSTD, OSPWORRIED

Show if: (OSP = 1:[Yes])

The next set of questions ask you about the other people you have had sex with recently.

Question: OSPID

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

20. During the last months, did you have sex with someone who injected drugs to get high?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPSO

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

21. During the last months, did you have sex with someone who was having sex with someone else besides you during the same time period?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPEX

Required

Show if: (OSPSO = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

22. Did any of these persons have sex with another person in exchange for money, drugs, goods, or services?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: OSPHIV

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

23. During the last months, did you have sex with someone who was HIV-infected?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: OSPHIVNC

Required

Show if: (OSPHIV = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

24. Did you have sex without a condom with any HIV-infected persons?

- ☐ Yes
☐ No
☐ Don't know
☐ Prefer not to answer

Question: OSPDR

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

25. During the last months, did you have sex with someone who was drunk or high on drugs while you were having sex with them?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPSTD

Required

Show if: (OSP = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
3	Don't know	
99	Prefer not to answer	

26. During the last months, did you have sex with someone who has recently been diagnosed with, or treated for one or more sexually transmitted infections?

- ☐ Yes
- ☐ No
- ☐ Don't know
- ☐ Prefer not to answer

Question: OSPWORRIED

Required

Show if: (OSPHIV = 2:[No]) or (OSPHIV = 3:[Don't know])

Scale Summary		
Code	Label	Show-If
1	Very worried	
2	Somewhat worried	
3	Not at all worried	
99	Prefer not to answer	

27. How worried are you that one or more of your sex partners may become infected with HIV in the next year?

- ☐ Very worried
- ☐ Somewhat worried
- ☐ Not at all worried
- ☐ Prefer not to answer

Collection: PPT_RISK_BEHAVIOR

Contains: ALCOH, ALCOHNUM, ALCOHB, VASDRUNK, IDUSE, IDNEEDLESHARE, MDKS, MS2HR, CRCO, CRCOS2HR, PRCO, PRCOS2HR, AMPMETH, AMPMETS2HR, METMAN, METMANS2HR, HERMED, HERMEDS2HR, MDMA, MDMAS2HR, WHO, WHOS2HR, POP, POPS2HR, OTHDRUG, OTHDRUG_FREQ, OTHDRUGS2HR, CIGVAPE, VASEX, HIVINFYR

The next set of questions ask about some other behaviors.

Question: ALCOH

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Monthly or less	
3	2-4 times a month	

4	2-3 times a week	
5	4 or more times a week	
99	Prefer not to answer	

28. During the last months, how often did you have a drink containing alcohol?

- ☐ Never
☐ Monthly or less
☐ 2-4 times a month
☐ 2-3 times a week
☐ 4 or more times a week
☐ Prefer not to answer

Question: ALCOHNUM

Required

Show if: (ALCOH ≠ 1:[Never]) and (ALCOH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	1 or 2	
2	3 or 4	
3	5 or 6	
4	7 to 9	
5	10 or more	
99	Prefer not to answer	

29. During the last months, on a typical day when you were drinking, how many standard drinks containing alcohol did you have?

- ☐ 1 or 2
☐ 3 or 4
☐ 5 or 6
☐ 7 to 9
☐ 10 or more
☐ Prefer not to answer

Question: ALCOHB

Required

Show if: (ALCOH ≠ 1:[Never]) and (ALCOH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Never	
2	Less than monthly	
3	Monthly	
4	Weekly	
5	Daily or almost daily	
99	Prefer not to answer	

30. During the last months, how often did you have 6 or more drinks on one occasion?

- ☐ Never
☐ Less than monthly
☐ Monthly
☐ Weekly
☐ Daily or almost daily
☐ Prefer not to answer

Question: VASDRUNK

Required

Show if: (SEXNUM.TEXT > 0) and (ALCOH ≠ 99:[Prefer not to answer]) and (ALCOH ≠ 1:[Never])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

31. During the last months, did you have sex while you were drunk?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: IDUSE

Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

32. During the last months, did you inject any drugs to get high?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: IDNEEDLESHARE

Required

Show if: (IDUSE = 1:[Yes])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

33. Did you share a needle with others?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: MDKS

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

34. During the last months, how often did you use Marijuana, dagga, K2, spice?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day

☐ Prefer not to answer

Question: MS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (MDKS ≠ 1:[Never]) and (MDKS ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

35. During the last months, did you have sex within 2 hours of you using marijuana?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: CRCO

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

36. During the last months, how often did you use crack cocaine?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: CRCOS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (CRCO ≠ 1:[Never]) and (CRCO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

37. During the last months, did you have sex within 2 hours of you using crack cocaine?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: PRCO

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	

4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

38. During the last months, how often did you use powder cocaine?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: PRCOS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (PRCO ≠ 1:[Never]) and (PRCO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

39. During the last months, did you have sex within 2 hours of you using powder cocaine?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: AMPMETH

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

40. During the last months, how often did you use amphetamine/methamphetamine, crystal meth, Khat/Cat, or tik?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: AMPMETS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (AMPMETH ≠ 1:[Never]) and (AMPMETH ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

41. During the last months, did you have sex within 2 hours of you using

amphetamine/methamphetamine, crystal meth, Khat/Cat, or tik?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: METMAN

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

42. During the last months, how often did you use methaqualone or mandrax?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: METMANS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (METMAN ≠ 1:[Never]) and (METMAN ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

43. During the last months, did you have sex within 2 hours of you using methaqualone or mandrax?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: HERMED

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

44. During the last months, how often did you use heroin, prescription pain killers/medications?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week

- ☐ Every day
- ☐ Prefer not to answer

Question: HERMEDS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (HERMED ≠ 1:[Never]) and (HERMED ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

45. During the last months, did you have sex within 2 hours of you using heroin, prescription pain killers/medications?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: MDMA

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

46. During the last months, how often did you use MDMA or Ecstasy?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: MDMA2HR

Required

Show if: (SEXNUM.TEXT > 0) and (MDMA ≠ 1:[Never]) and (MDMA ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

47. During the last months, did you have sex within 2 hours of you using MDMA or Ecstasy?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: WHO

Required

Scale Summary		
Code	Label	Show-If

1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

48. During the last months, how often did you use whoonga/wunga or nyaope?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: WHOS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (WHO ≠ 1:[Never]) and (WHO ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

49. During the last months, did you have sex within 2 hours of you using Whoonga/wunga or nyaope?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: POP

Required

Scale Summary		
Code	Label	Show-If
1	Never	
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

50. During the last months, how often did you use poppers?

- ☐ Never
- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: POPS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (POP ≠ 1:[Never]) and (POP ≠ 99:[Prefer not to answer])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	

99 Prefer not to answer

51. During the last months, did you have sex within 2 hours of you using Poppers?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: OTHDRUG

Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	Not applicable - No other drugs used	
99	Prefer not to answer	

52. During the last months, have you used any other drugs? If yes, please specify.

- ☐ Yes
- ☐ Not applicable - No other drugs used
- ☐ Prefer not to answer

Question: OTHDRUG_FREQ

Required

Show if: (OTHDRUG = 1:[Yes])

Scale Summary		
Code	Label	Show-If
2	Once per week or less	
3	2-3 times a week	
4	4-6 times a week	
5	Every day	
99	Prefer not to answer	

53. During the last months, how often did you use ?

- ☐ Once per week or less
- ☐ 2-3 times a week
- ☐ 4-6 times a week
- ☐ Every day
- ☐ Prefer not to answer

Question: OTHDRUGS2HR

Required

Show if: (SEXNUM.TEXT > 0) and (OTHDRUG_FREQ ≠ 99:[Prefer not to answer]) and (OTHDRUG_FREQ was answered)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

54. During the last months, did you have sex within 2 hours of you using ?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: CIGVAPE

Required

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

55. Do you currently smoke cigarettes or e-cigs (Vape)?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: VASEX

Required

Show if: (SEXNUM.TEXT > 0)

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

56. In the last months, have you given and/or received money, gifts, drugs, goods, shelter, or services in exchange for sex?

- ☐ Yes
- ☐ No
- ☐ Prefer not to answer

Question: HIVINFYR

Required

Show if: (SCHEDULE = 1:[Schedule 1]) or (SCHEDULE = 4:[Schedule 4])

Scale Summary		
Code	Label	Show-If
1	Not at all likely	
2	Somewhat unlikely	
3	Neutral/No opinion	
4	Somewhat likely	
5	Extremely Likely	
99	Prefer not to answer	

57. How likely do you think it is that you may become infected with HIV in **the next year**?

- ☐ Not at all likely
- ☐ Somewhat unlikely
- ☐ Neutral/No opinion
- ☐ Somewhat likely
- ☐ Extremely Likely
- ☐ Prefer not to answer

Collection: STUDY_PRODUCT

Contains: ANTIPLAC, HIGHLOW, INVINFUSION

Show if: (SCHEDULE = 1:[Schedule 1]) or (SCHEDULE = 4:[Schedule 4])

Question: ANTIPLAC

Required

Show if: (VISIT is-any-of 09.0:[Visit 09.0 (Infusion #4)] or 15.0:[Visit 15.0 (Infusion #7)] or 21.0:[Visit 21.0 (Infusion #10)] or 26.0:[Visit 26.0 (End Visit)] or 72.0:[Visit 72.0] or 74.0:[Visit 74.0] or 76.0:[Visit 76.0] or 78.0:[Visit 78.0])

Scale Summary		
Code	Label	Show-If

1	VRC01	
2	Placebo	
3	Don't know	
99	Prefer not to answer	

58. Do you think you received the VRC01 antibody or placebo in this study?

- ☐ VRC01
☐ Placebo
☐ Don't know
☐ Prefer not to answer

Question: HIGHLOW

Required

Show if: (ANTIPLAC = 1:[VRC01])

Scale Summary		
Code	Label	Show-If
1	High Dose	
2	Low Dose	
3	Unsure	
99	Prefer not to answer	

59. Do you think you received the high dose, low dose, or are you unsure?

- ☐ High Dose
☐ Low Dose
☐ Unsure
☐ Prefer not to answer

Question: INVINFUSION

Required

Show if: (VISIT = 02.0:[Visit 02.0 (Enrollment/Infusion #1)])

Scale Summary		
Code	Label	Show-If
1	Yes	
2	No	
99	Prefer not to answer	

60. Have you, a family member, or close friend ever had an IV infusion?

- ☐ Yes
☐ No
☐ Prefer not to answer

References

- Aalen, O. (1978), “Nonparametric Inference for a Family of Counting Processes,” *The Annals of Statistics*, 6, 701–726.
- Andersen, P., Borgan, O., Gill, R., and Keiding, N. (1993), *Statistical Models Based on Counting Processes*, Berlin and New York: Springer.
- Benkeser, D., Carone, M., and Gilbert, P. B. (2016), “Efficient and robust estimation of cumulative incidence in the presence of competing risks,” *submitted*.
- Breiman, L. (2001), “Random forests,” *Machine learning*, 45, 5–32.
- Breiman, L., Friedman, J. H., Olshen, R. A., and Stone, C. I. (1984), *Classification and regression trees*, Belmont, Calif.: Wadsworth.
- Castillo-Mancilla, J. R., Zheng, J.-H., Rower, J. E., Meditz, A., Gardner, E. M., Predhomme, J., Fernandez, C., Langness, J., Kiser, J. J., Bushman, L. R., and Anderson, P. L. (2013), “Tenofovir, Emtricitabine, and Tenofovir Diphosphate in Dried Blood Spots for Determining Recent and Cumulative Drug Exposure,” *AIDS Research and Human Retroviruses*, 29, 384–390.
- Follmann, D. and Huang, C.-Y. (2015), “Incorporating founder virus information in vaccine field trials,” *Biometrics*, 71, 386–396.
- Freidlin, B., Korn, E. L., and Gray, R. (2010), “A general inefficacy interim monitoring rule for randomized clinical trials,” *Clinical Trials*, 7, 197–208.
- Gilbert, P., Grove, D., Gabriel, E., Huang, Y., Gray, G., Hammer, S., et al. (2011), “A sequential Phase 2b trial design for evaluating vaccine efficacy and immune correlates for multiple HIV vaccine regimens,” *Statistical Communications in Infectious Diseases*, 3.
- Gilbert, P. B., Wei, L. J., Kosorok, M. R., and Clemens, J. D. (2002), “Simultaneous Inferences on the Contrast of Two Hazard Functions with Censored Observations,” *Biometrics*, 58, pp. 773–780.
- Grambsch, P. M. and Therneau, T. M. (1994), “Proportional hazards tests and diagnostics based on weighted residuals,” *Biometrika*, 81, 515–526.
- Grant, R. M., Anderson, P. L., McMahan, V., Liu, A., Amico, K. R., Mehrotra, M., Hosek, S., Mosquera, C., Casapia, M., Montoya, O., Buchbinder, S., Veloso, V. G., Mayer, K., Chariyalertsak, S., Bekker, L.-G., Kallas, E. G., Schechter, M., Guanira, J., Bushman, L., Burns, D. N., Rooney, J. F., Glidden, D. V., and iPrEx study team (2014), “Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study,” *The Lancet. Infectious Diseases*, 14, 820–829.

- Hammer, S. M., Sobieszczyk, M. E., Janes, H., Karuna, S. T., Mulligan, M. J., Grove, D., Koblin, B. A., Buchbinder, S. P., Keefer, M. C., Tomaras, G. D., Frahm, N., Hural, J., Anude, C., Graham, B. S., Enama, M. E., Adams, E., DeJesus, E., Novak, R. M., Frank, I., Bentley, C., Ramirez, S., Fu, R., Koup, R. A., Mascola, J. R., Nabel, G. J., Montefiori, D. C., Kublin, J., McElrath, M. J., Corey, L., Gilbert, P. B., and Team, H. . S. (2013), “Efficacy Trial of a DNA/rAd5 HIV-1 Preventive Vaccine,” *New England Journal of Medicine*, 369, 2083–2092.
- Hernán, M. Á., Brumback, B., and Robins, J. M. (2000), “Marginal structural models to estimate the causal effect of zidovudine on the survival of HIV-positive men,” *Epidemiology*, 11, 561–570.
- Heyse, J. F., Kuter, B. J., Dallas, M. J., Heaton, P., and Team, R. S. (2008), “Evaluating the safety of a rotavirus vaccine: the REST of the story,” *Clinical Trials*, 5, 131–139.
- Holm, S. (1979), “A Simple Sequentially Rejective Multiple Test Procedure,” *Scandinavian Journal of Statistics*, 6, 65–70.
- Juraska, M. and Gilbert, P. (2013), “Mark-specific hazard ratio model with multivariate continuous marks: An application to vaccine efficacy,” *Biometrics*, 69, 328–337.
- Parzen, M., Wei, L., and Ying, Z. (1997), “Simultaneous confidence intervals for the difference of two survival functions,” *Scandinavian Journal of Statistics*, 24, 309–314.
- Schoenfeld, D. (1983), “Sample-size formula for the proportional-hazards regression-model,” *Biometrics*, 39, 499–503.
- Stekhoven, D. J. and Bühlmann, P. (2011), “MissForest—non-parametric missing value imputation for mixed-type data,” *Bioinformatics*, 28, 112–118.
- van der Laan, M. J., Polley, E. C., and Hubbard, A. E. (2007), “Super learner,” *Statistical Applications in Genetics and Molecular Biology*, 6, 1–23.

**Statistical Analysis Plan for Assessing Correlates of
Prevention Efficacy in the HVTN 704/HPTN 083 and
HVTN 703/HPTN 081 Antibody Mediated Prevention
Phase 2b Prevention Efficacy Trials, with Focus on
Neutralization Sieve Analysis**

Allan deCamp, Yunda Huang, Michal Juraska, Erika Rudnicki, Lily Zhang,
Peter B. Gilbert

October 15, 2020

Version 1.0

Contents

1	Introduction	3
1.1	Cohorts for marker analyses	4
2	Overview of AMP Correlates Analyses and What We Expect to Learn	4
2.1	Identification of the most frequent virus variant	6
3	Phenotypic/neutralization sieve analysis	6
3.1	Definitions of neutralization resistance markers for phenotypic/neutralization sieve analysis and descriptive analyses	7
3.2	Two inferential statistical approaches to phenotypic/neutralization sieve analysis . .	8
3.2.1	Approach A: Compare mean neutralization resistance markers across treatment arms in HIV-1 infected cases	8
3.2.2	Approach B: Assess prevention efficacy by neutralization resistance marker of the infecting virus(es)	11
3.3	Multiple hypothesis testing adjustment for phenotypic/neutralization sieve analysis .	14
4	Analysis of VRC01 vs. Placebo Effect on Viral Load at First HIV-1 RNA PCR Positive Time point	15

1 Introduction

This marker statistical analysis plan (SAP) will be implemented for each of the AMP efficacy trials separately, as well as pooling data sets across the two efficacy trials. The latter analyses are important for improving precision, and use of the same study design and protocol for the two trials means that it is possible to combine the data and obtain interpretable answers.

AMP Secondary Objective 1 from the protocol: To develop a marker(s) of the VRC01 mAb that correlates with the level and antigenic specificity of protection against HIV-1 infection and to provide insight into the mechanistic correlates of protection

Endpoints for Secondary Objective 1 from the protocol:

1. Serum concentration of VRC01 (ELISA and/or Drug Levels/Luminex Platform, TZM-bl target cell neutralizing antibody assay)
2. Serum mAb effector functions to HIV-1 Envs representing variability of the VRC01 antibody footprint
3. Sequences of breakthrough HIV-1 infections from the earliest available HIV-positive plasma samples
4. VRC01 neutralization-sensitivity of, and other effector function against, HIV-1 strains from infected trial participants from the earliest available post-HIV-1-infection serum samples

The current manuscript assessed secondary objective 4 listed above, through neutralization sieve analysis.

Marker Type V_{obs}

This SAP considers analysis of a type of biomarker, with notation V_{obs} , ascribed to a feature of an HIV-1 isolate measured from an AMP participant experiencing the primary HIV-1 infection endpoint.

- V_{obs} : Features of breakthrough infecting HIV-1s at the observed time of the first HIV-1 RNA positive sample
 - AA sequence features (e.g., AA patterns of positions constituting the VRC01 footprint, or AA patterns known to affect functional or structural interactions of VRC01 and HIV-1)
 - Phenotypic features defined by level of neutralization sensitivity to VRC01, as measured by the TZM-bl target cell assay (e.g., IC50, IC80)

The current manuscript focuses on assessment of V_{obs} defined by the latter approach (TZM-bl target cell assay neutralization resistance level).

Section 3.1 lists the neutralization phenotype features that are studied.

1.1 Cohorts for marker analyses

One or more of the following cohorts are used for performing the main analyses that do not include HIV-1 infection events with diagnosis date after the Week 80 study visit.

- **MITT Marker Cohort:** The subset of the MITT cohort that is selected into the case-control study for measurement of VRC01 concentrations.
- **MITT Cases:** The subset of the MITT cohort that has a registered primary HIV-1 infection endpoint.
- **MITT Cases for AA Sequence Sieve Analysis:** The subset of the MITT Cases that have available data on HIV-1 gp160 amino acid sequences.
- **MITT Cases for Phenotypic Sieve Analysis:** The subset of the MITT Cases that have available data on sensitivity of one or more virus isolates to neutralization by the clinical lot of VRC01.

The current manuscript focuses on analysis of the MITT Cases for Phenotypic Sieve Analysis cohort, including all primary HIV-1 infection endpoints with virus neutralization resistance testing data available.

2 Overview of AMP Correlates Analyses and What We Expect to Learn

The key concept in the AMP trials has been to define the concentration of VRC01 that is required to reduce acquisition of infection. This endpoint can be interrogated in several ways, most simply by the primary objective of whether VRC01 reduces acquisition overall compared to placebo, and by the secondary objective of whether higher dose VRC01 reduces acquisition more than lower dose VRC01. Several other analyses are planned to assess more specifically the level of neutralizing antibody titer in serum that blocks viruses that are measured to be sensitive to the antibody. The following list summarizes the planned analyses and what we expect to learn, although this manuscript only reports the results on the phenotypic/neutralization sieve analysis, given that the data sets needed for the other analyses are not yet available. The serum concentration and serum neutralization correlates of risk analyses will be conducted later after the data are available from the complete case-control sample.

1. **Serum Concentration Correlates of Risk (CoR) Analyses** address how VRC01 serum concentration correlates with instantaneous risk of HIV-1 acquisition? We expect to learn concentration thresholds at which risk of HIV-1 acquisition is low and VRC01 prevention efficacy is inferred to be high.
2. **Serum Neutralization CoR Analyses** are similar to Concentration CoR analyses, except the concentration marker is exchanged for predicted neutralization titer (ID_{50} or ID_{80}) to a given Env pseudovirus or averaged to a panel of Env pseudoviruses. By taking the panel to be breakthrough infecting viruses of placebo recipients, we expect to learn levels of serum neutralization against typical/representative exposing viruses that are associated with low HIV-1 risk and thus likely high VRC01 prevention efficacy. These putative protective levels

may then be used as the primary endpoint in future phase 1 trials of bnAb-inducing vaccine regimens.

3. **Phenotypic/Neutralization Sieve Analysis** addresses how the level of VRC01 prevention efficacy to block HIV-1 acquisition depends on the VRC01 neutralization resistance level of breakthrough founder viruses (e.g., IC50 or IC80 or the reciprocal of instantaneous inhibitory potential (IIP) (Shen, Siliciano et al., 2008, Nature Medicine) of the most-sensitive or least-sensitive virus isolate in the set of isolates with IC50 and IC80 data for a given infected case). Neutralization sieve analysis directly informs on what constitutes sufficient sensitivity of an exposing virus for VRC01 to block infection acquisition.
4. **Amino Acid Sequence Sieve Analysis** addresses how the level of VRC01 prevention efficacy to block HIV-1 acquisition depends on Env gp160 amino acid features that are known to be part of the VRC01 footprint or otherwise known to predict VRC01 neutralization sensitivity. We expect (1) to learn whether a proteomic antibody resistance score based on Env gp160 amino acids discriminates prevention efficacy as well or better than neutralization measurements (IC50 and IC80), and (2) to learn specific amino acid patterns that are important for discriminating VRC01 prevention efficacy.
5. **Integrated Correlates of Risk/Sieve Analyses** focus on the critical issue that the two key parameters that are hypothesized to impact prevention efficacy – concentration at exposure and virus neutralization sensitivity at exposure – are best addressed in an integrated fashion. The analyses assess how Concentration CoRs vary with IC50 or IC80 thresholds of the breakthrough founder virus, interrogating the hypothesis that HIV-1 can readily transmit if either concentration is low or the exposing virus is neutralization resistant, but otherwise VRC01 efficiently blocks transmission. Specifically, the Concentration CoR analyses (Approaches 3–5) will be repeated restricting to sensitive viruses (defined as $IC_{50} < 1\mu g/ml$ or as $IC_{80} < 1\mu g/ml$) and restricting to non-sensitive viruses ($IC_{50} \geq 1\mu g/ml$ and as $IC_{80} \geq 1\mu g/ml$).

Summary of how the sieve analyses work. For each HIV-1 infected case, bulk sequencing is performed on the first HIV-1 RNA+ PCR sample to produce a consensus Env gp160 sequence. If there is evidence of multiple founder viruses, then approximately 20 gp160 sequences are measured by single genome sequencing. The most-frequent virus variant and all minority virus variants (at frequency $> 10\%$) are studied for their neutralization resistance level to VRC01 (the clinical lot) in the TZM-bl target cell assay, where the neutralization resistance level is measured by IC50 and IC80, and the IIP (defined below); we refer to IC50, IC80, and IIP as neutralization resistance markers. Neutralization sieve analysis proceeds by estimating how VRC01 prevention efficacy depends on IC50, IC80, and IIP, where IIP is a function of IC50, IC80, and a clinically relevant VRC01 concentration. In particular, IIP is defined in Wagh et al. (2016, 2018), as

$$IIP = -\log_{10}(1 - f(c)), \quad (1)$$

where $f(c)$ is the fraction neutralization at concentration c :

$$f(c) = c^m / (IC_{50}^m + c^m),$$

with slope $m = \log_e(4)/(\log_e IC_{80} - \log_e IC_{50})$. The analysis is conducted setting c to be the median mid-point concentration across all VRC01 recipients, including all mid-point visits with a prior infusion, and calculated separately for each trial and dose group.

2.1 Identification of the most frequent virus variant

The first step of the sequence-selection process was Sanger sequencing of a 2.9 kb segment covering *rev/env/nef* and generating the consensus sequence. Looking only at nucleotide sites with non-synonymous variability, if 0 or 1 double-peaks are observed on the sequencing chromatogram, then the sequences can be represented by 1–2 majority variants. These 1–2 majority variants were sent to Genewiz for *rev-env* gene synthesis.

Of sequences selected this way, if only one sequence was selected, it was deemed the most frequent variant. If two sequences were selected, the most frequently occurring of these two sequences was deemed the most frequent variant.

If more than one double-peak was observed at the non-synonymous sites, then the sequence diversity is more nuanced, and a similar 2.9 kb *rev/env/nef* region was sequenced from the sample via PacBio or Sanger-SGA sequencing. A phylogenetic tree was built from the sequences, and a sequence was selected for synthesis if it was the most commonly occurring strain in a cluster representing at least 10% of the sequence population.

Of sequences selected this way, the most frequent sequence was deemed the most common variant.

Some samples included additional variants not well characterized by clusters with 10% or more representation, possibly due to CTL pressure, high diversity, or recombination. For these ambiguous cases, a system called “CLUST” was used, which implemented the following process:

1. Note all variants with 10% or greater AA frequency (i.e., the initial rule).
2. Iterate through all remaining variants, keeping anything that has at least eight different AAs from the variants noted above, and has a genotype that is observed at least twice.
3. If this results in a list of four or more sequences, increase the distance threshold by one AA and repeat. This caps the list to a maximum of four sequences.

In one case, in HVTN 704/HPTN 085, there were no variants that exceeded the 10% threshold. For this instance, the most common variant (3.8%) was chosen.

Other issues affected this process. For example, some sequences were unable to be synthesized by Genewiz, resulting in either no genes synthesized or the synthesis of sequences that were not majority virus variants.

3 Phenotypic/neutralization sieve analysis

Phenotypic/neutralization sieve analysis is conducted based on functional infectious molecular gp160 clones made for each primary endpoint HIV-1 infected case, based on the sole, most frequent, most in vitro sensitive, or most in vitro resistant gp160 variant sampled at the first HIV-1

RNA positive time point (with in vitro resistance level measured by IC_{50} or IC_{80} from the TZM-bl target cell assay). The neutralization TZM-bl target cell assay is applied to study functional properties of each Env pseudovirus in its interaction with VRC01.

Due to a lack of knowledge guiding the relative importance of different ways to choose a viral variant from among a set of viral variants with IC_{50} / IC_{80} / IIP data, the common analysis strategy involves conducting a sensitivity-type analysis, in which the sieve analysis methods will be applied using a single virus for each infected case, defined as (1) the most frequent virus variant; (2) the most sensitive virus variant (e.g., the variant with minimum IC_{50} or minimum IC_{80}); and (3) the least sensitive founder virus (e.g., the variant with maximum IC_{50} or maximum IC_{80}) from the first HIV-1 RNA+ time point from each endpoint case. The variants (2) and (3) will be determined by ranking an individual's set of virus variants by the given neutralization resistance marker.

For variant (2), we expect it is highly likely for prevention efficacy against viruses with neutralization resistance level marker IC_{50} or IC_{80} value v [$PE(v)$] for large values of v to be zero, given that all virus variants in the case's set of isolates are resistant. For variant (3), $PE(v)$ for the smallest IC_{50} or IC_{80} value v represents infections with viruses that are all highly sensitive to VRC01, such that $PE(v = 0)$ has the greatest chance of being large, if the TZM-bl target cell assay is able to discriminate in vivo prevention efficacy. In contrast, for variant (2), the value of $PE(v)$ for the smallest IC_{50} or IC_{80} value v has more uncertainty, given that some of the viruses in the set of virus variants in the case's set of isolates may be resistant; similarly, for variant (3) it is uncertain whether $PE(v)$ for high values of v will be zero, because some of the variants in the set of founders may be sensitive to VRC01. Yet, if $PE(v)$ if variant (2) is zero for moderately large v , it supports that minority resistant variants ruin VRC01 efficacy – thus assessing variant (3) $PE(v)$ is appropriate from a pre-test concern that VRC01 may not be able to protect against quasispecies challenge unless the whole set of challenge viruses are sensitive. As such, the analyses focus on reporting analyses by variant (3), while including the analyses of approaches (1) and (2) to handling multiple-isolate cases as sensitivity analyses.

3.1 Definitions of neutralization resistance markers for phenotypic/neutralization sieve analysis and descriptive analyses

Experimental serum neutralization titers in AMP, for a given virus against the VRC01 clinical lot, are measured using six replicates aggregated across two starting concentrations (100 μ g/ml and 5 μ g/ml). First, the mean of the log titers is estimated using censored linear regression to account for values above and below the limits of detection. Next, the mean log titer is exponentiated to calculate the geometric mean titer. If the IC_{50} (or IC_{80}) is not well captured by both starting concentrations, the censored linear regression estimation may fail to converge. In these cases, we restrict to three replicates from the single starting concentration that best captures the IC_{50} (or IC_{80}). For each isolate and neutralization threshold, this summary measure is referred to as the IC_{50} titer (or IC_{80} titer).

Experimental neutralization readouts are measured for each VRC01 group case's serum sample at the first HIV-1 RNA+ time point and the two previous time points against his/her own breakthrough HIV-1 (sampled at the first HIV-1 RNA positive time point). Functional readouts of the clinical lot of VRC01 against all constructed Env pseudoviruses for HIV-1 infected cases (from all

treatment groups) are also measured, which provides a way to predict the neutralization readout of each serum sample against every constructed Env.

The set of neutralization resistance markers characterizing breakthrough founder Env pseudoviruses that will be analyzed, and distributions graphed by treatment arm and trial, are the following:

1. $\log_{10}$ IC50
2. $\log_{10}$ IC80
3. IIP [defined at (1)] at the median mid-point visit concentration for a given study and dose group
4. Ordered 3-category phenotype in vitro Sensitive, Intermediate, Resistant based on IC_{50} , defined by ranges $IC_{50} < 1\mu g/ml$, $1-3\mu g/ml$, and $> 3\mu g/ml$, respectively
5. Ordered 3-category phenotype in vitro Sensitive, Intermediate, Resistant based on IC_{80} , defined by ranges $IC_{50} < 1\mu g/ml$, $1-3\mu g/ml$, and $> 3\mu g/ml$, respectively

The marks IC50, IC80, IIP, are analyzed using the most resistant, most sensitive, and most frequent viral variant of the measured variants for a given case. For descriptive analysis of how the mark variant affects potential results, ‘pairs scatterplots’ will be made for the nine markers defined by (IC50, IC80, IIP) cross-classified with (most resistant, most sensitive, most frequent) viral variant. The pairs plots will be made separately for each AMP trial and for the AMP trials pooled. For each plot, the covariate-adjusted Spearman rank correlation will be affixed to the plot, calculated using Bryan Shepherd et al.’s PResiduals R package. Each analysis adjusts for treatment arm; the 704/085 analysis also adjusts for South America vs. not South America; the AMP trials pooled analysis also adjusts for trial.

3.2 Two inferential statistical approaches to phenotypic/neutralization sieve analysis

For statistical analysis, two approaches to phenotypic sieve analysis are employed. Each of the phenotypic sieve analyses is done three times, for each of the three ways to accommodate multiple neutralization resistance marker values from multiple-isolate HIV-1 infected cases as described in Section 3.

3.2.1 Approach A: Compare mean neutralization resistance markers across treatment arms in HIV-1 infected cases

Approach A compares geometric mean (for IC50, IC80) or mean (for IIP) neutralization resistance marker values between the VRC01 group viruses and the placebo group viruses; such neutralization sieve analysis has been conducted previously in HIV-1 vaccine efficacy trials (Gilbert, deCamp, et al., 2010; Montefiori, 2014). This approach will be applied using doubly robust targeted minimum loss-based estimation (DRTMLE) for a quantitative readout (Benekser et al., 2017), to estimate the mean readout of each group with a Wald 95% confidence interval, as well as the mean difference (VRC01 - placebo) with a Wald 95% confidence interval (and transforming results to the geometric mean and geometric mean ratio scale for IC50 and IC80). In addition, the mean readouts of the placebo, lower dose VRC01, and higher dose VRC01 groups are studied, to assess dose-response. For

these analyses, 95% confidence intervals are presented around the VRC01 pooled and treatment-arm specific means and around each mean difference (VRC01 pooled vs. placebo, low dose vs. placebo, and high dose vs. placebo), but p-values are not used (we limit the number of pre-specified p-values to those calculated under Approach B). If some HIV-1 infected cases are missing data on the IC50, IC80, or IIP marker under study, the DRTMLE method will accommodate the missing data by including a model of the probability of observing the marker, where the model will be simpler if there is less missing data.

In addition, all implementations of the DRTMLE method adjust for baseline covariates that are judged to possibly be associated with both HIV-1 infection and with the assay readout for a virus. Analyses for each trial adjust for each, with the HVTN 704/HPTN 085 analysis also adjusting for South America vs. not South America and HVTN 703/HPTN 081 also adjusting for South Africa vs. not South Africa; these variables could plausibly be dual predictors of both HIV-1 infection and the marker outcome. The trials-pooled analyses also adjust trial. This covariate-adjustment is needed because the analysis must control for all dual predictors of HIV-1 infection and the assay readout endpoint in order that the estimated contrast in means across treatment arms assesses a causal effect in the sub-population of participants who would be HIV-1 infected under either treatment assignment (VRC01 or placebo) (e.g., Shepherd et al., 2006). The covariate-adjustment is achieved using a superlearner model for the conditional outcome regression (with the mark the outcome), fit using the non-negative least squares (NLLS) loss function (the default for the SuperLearner R package with a quantitative outcome), and including the following learners for predicting a quantitative outcome (as hard-coded into the Superlearner R package): SL.mean, SL.glm, SL.glm.interaction, SL.glmnet, SL.ksvm, and SL.nnet. All of these learners are documented in the SuperLearner R package, for example SL.mean fits a sample mean, SL.glm fits a standard linear regression, SL.glm.interaction fits a linear regression with all 2-way interactions, and SL.glmnet fits a LASSO model for a quantitative outcome selecting λ via cross validation such that error is within one standard error of the minimum.

For analyses with missing mark data a superlearner model with negative binomial log likelihood-loss is used to estimate the probability of observing the mark. If fewer than 20% of cases are missing marks, then the library of learners is small, only including SL.mean and SL.glm (with logistic link). If between 20% and 40% of cases are missing marks, then the library is expanded to also include SL.step, SL.bayesglm (with logistic link), SL.glm (with logistic link), SL.gam, SL.glm.interaction (with logistic link), and SL.glmnet (with logistic link). If more than 40% of cases are missing marks (which could occur in ‘Quadrant analyses’), then the library is further expanded to include SL.earth, SL.xgboost, and SL.ranger. For example, SL.mean function fits a sample mean, SL.step performs a stepwise selection logistic regression optimizing AIC, SL.glm.interaction fits a logistic regression with all 2-way interactions and SL.glmnet fits a LASSO model for a binary outcome selecting λ via cross validation such that error is within one standard error of the minimum. The amount of missing mark data was less than 10%, such that SL.mean and SL.glm were used.

Details on R code implementing the DRTMLE Approach A phenotypic sieve analysis. The analysis will be done using the *drtmle* R package by Dr. David Benkeser available at CRAN. Superlearner is used to estimate the propensity score for treatment assignment to VRC01 vs. placebo, using logistic regression and lasso regression in the library of learners (SL.mean, SL.glm, SL.glmnet in the Superlearner R package).

The code accomplishes the following two tasks that would be reported (using the mark IC80 for concreteness):

1. Report point and 95% confidence interval estimates of the geometric mean IC80 for the VRC01 groups pooled, the placebo group, the high dose VRC01 group, and the low dose VRC01 group.
2. Report point and 95% CI estimates of the IC80 geometric mean ratio, for VRC01 groups pooled vs. placebo, for VRC01 high dose vs. placebo, and for VRC01 low dose vs. placebo.

The following README file on the SCHARP network drives describes the computer code for implementing the DRTMLE data analyses:

```
T:\vaccine\p704\analysis\efficacy\code\  
NonparametricSmoothingPHsieveanalysisSunetal2015\  
READMEcodeforimplementingApproachADRTMLEforAMPfinalreporting.txt
```

The data analyses set IC50 and IC80 values >100 to 100, given that these are outlying values that are marked to be highly resistant to neutralization by VRC01, and keeping the high outlying values would introduce undue influence on estimation and inference on means.

We list the data analysis code for the IC80 neutralization resistance marker, which shows the pre-specified input parameters, which include the utilized superlearner libraries for the propensity score (probability of assignment to VRC01), whether the mark is missing, and the outcome ($\log_{10}$ IC80) regression (see DRTMLE R package documentation for additional details). Default settings are used for the superlearner algorithms. The same input parameter specifications are used for the 704/085, 703/081, and 703/081+704/085 data analyses.

```
# Example analysis of HVTN 704/HPTN 085  
# All continuous covariates are pre-standardized to have empirical  
# mean 0 and variance 1.  
#A = 1 if assigned to receive VRC01 (at either dose); 0 if assigned placebo  
#W = a data frame with variables for predicting Y  
#704/085 data analysis: W = (W1,W2) with  
#W1 = Age (in years) at enrollment  
#W2 = 1 if South America, 0 if not South America  
#703/081 data analysis: W = (W1,W2) with  
#W1 = Age (in years) at enrollment  
#W2 = 1 if South Africa, 0 if a different country from South Africa  
#703/081+704/085 data analysis: W = (W1,W2,W3,W4) with  
#W1 = Age (in years) at enrollment  
#W2 = Indicator of 704/South America (reference category 704/not South America)  
#W3 = Indicator of 703/South Africa (reference category 704/not South America)  
#W4 = Indicator of 703/not South Africa (reference cat. 704/not South America)  
#Y = mark of interest (e.g. log10 IC80)
```

```
sieve_fitAic80 <- drtmle(W = W, A = A, Y = Y, stratify=FALSE,  
                        SL_g = list(A = c("SL.mean", "SL.glm", "SL.glmnet"),
```

```

DeltaY = c("SL.mean", "SL.glm")),
SL_Q = c("SL.mean", "SL.glm", "SL.glm.interaction", "SL.glmnet", "SL.ksvm", "SL.nnet"),
      glm_Qr = "gn",
      glm_gr = "Qn", cvFolds = 1,
      SL_method = "method.NNLS", family = gaussian(), returnModels = TRUE)

# For each analysis high-dose VRC01 vs. placebo, and low-dose
# VRC01 vs. placebo, the above code is repeated.

```

3.2.2 Approach B: Assess prevention efficacy by neutralization resistance marker of the infecting virus(es)

Approach A to phenotypic sieve analyses conditions on HIV-1 infection, and therefore the results are not interpretable in terms of how prevention efficacy depends on phenotypic HIV-1 characteristics. For a complementary analysis without this limitation, we also implement Approach B, which conducts phenotypic sieve analyses based on prospective prevention efficacy parameters. Because of the interpretation in terms of prospective prevention efficacy, the Approach B sieve analyses are prioritized and p-values are included.

We consider two estimands for measuring neutralization-feature specific prevention efficacy:

- $PE_h(v)$ defined as one minus the hazard ratio (VRC01 [dose-pooled or dose-specific]/placebo) of the primary study endpoint through the week 80 visit with a specific value $V_{obs} = v$ of IC50, IC80, or IIP associated with the measurements made on one or more HIV-1 isolates from the infected participant's earliest HIV-1 RNA+ sample,
- $PE_c(\tau, v)$ defined as one minus the ratio (VRC01 [dose-pooled or dose-specific]/placebo) of cumulative incidences at time τ of the primary study endpoint with a specific value $V_{obs} = v$ of IC50, IC80, or IIP associated with the measurements made on one or more HIV-1 isolates from the infected participant's earliest HIV-1 RNA+ sample. The identical timepoints τ are selected as in the primary overall trial-specific and trial-pooled prevention efficacy analyses (87.0 weeks for 704/085, 85.9 weeks for 703/081, and 85.9 weeks for trials-pooled).

A neutralization sieve effect is defined as statistically significant evidence for differential PE across multiple levels of the mark variable being analyzed. The primary estimand of interest will be $PE_h(v)$, and sieve effect evidence will be evaluated for every specified feature V_{obs} with respect to $PE_h(v)$. Additionally, for the 3-level ordered category neutralization mark, we will also evaluate neutralization sieve effect evidence in parallel based on the estimand $PE_c(\tau, v)$. This analysis is done because neutralization phenotypes will help provide insight into the primary overall cumulative PE result for the primary analysis estimand $PE_c(\tau)$ defined as one minus the overall cumulative incidence ratio at τ .

We use published sieve analysis methods for analyzing various types of neutralization resistance markers V_{obs} . For the 3-category ordered categorical V_{obs} , the Aalen-Johansen nonparametric maximum likelihood estimator is used for assessing $PE_c(\tau, v)$ for each of the three levels v of V_{obs} (with 95% CIs, 2-sided p-values for $PE_c(\tau, v)$ departing from 0% for a given v , and a 1-sided p-value for a linear trend in $\log\{1 - PE_c(\tau, v)\}$ with v). For quantitative/approximately continuous V_{obs}

with a large number of levels such as IC50, IC80, IIP, the Juraska and Gilbert (2013) method, implemented in the `sievePH` R package available on CRAN, is used along with the goodness-of-fit diagnostics for the modeling assumptions. In addition, the nonparametric kernel smoothing method of Sun, Gilbert, and McKeague (2009) will be applied, where the smoothing may yield additional insights. The analysis will be implemented using the `cmprskPHContinMark` R code available at Dr. Peter Gilbert’s website.

If more than 10 percent of HIV-1 infected cases are missing neutralization resistance marker data, then the missing data versions of the methods will be used, which means replacing Juraska and Gilbert (2013) with the augmented inverse probability weighting (AIPW) method of Juraska and Gilbert (2016) and replacing Sun, Gilbert, and McKeague (2009) with the AIPW methods of Sun and Gilbert (2012) and Gilbert and Sun (2015) (the former paper describing estimation and the latter paper describing hypothesis testing). If needed, these missing data methods will be implemented estimating the probability of observing the mark using a best-fitting logistic regression model selected by all-subsets model selection according to the BIC criterion; where the covariates considered are treatment, South America vs. not South America, and trial. In addition, for each candidate auxiliary variable, linear or logistic regression will be used to relate the mean of the auxiliary variable to the variables retained in the “missing data model”, treatment, and the mark, where again BIC is used to pick a best-fitting model. The Gilbert and Sun (2015) AIPW method will be applied to test H_{10} vs. H_{1m} and to test H_{20} vs. H_{2m} , using the notation of the paper. The same bandwidth procedure will be used as described for the estimation. If less than 10 percent of HIV-1 infected cases are missing mark data, then simpler complete-case implementations of the methods will be used, which are the Juraska and Gilbert (2013) and Sun, Gilbert, and McKeague (2009)/Gilbert and Sun (2015) methods, as noted above.

For trial-specific analyses involving $PE_c(\tau, v)$ comparing dose-pooled VRC01 vs. placebo, the estimator for cumulative incidence in the dose-pooled VRC01 group will be stratified by VRC01 dose group, i.e., the VRC01 group estimate will be an average of the two dose-specific estimates, with an equal weight assigned to each dose group. For trial-pooled analyses, the competing risks Cox model, the duplication method Cox model underlying the Lunn and McNeil (1995) calculations, and the Cox model portion underlying the product estimator will be stratified by trial (i.e., have a separate baseline hazard for each trial), whereas the cumulative incidence estimator will be stratified by the combination of treatment group and trial. For PE_h , stratification is by separate baseline hazards (the estimating equation portion of the product estimator is unstratified), and, for PE_c , stratification is by separate cumulative incidence estimation in each stratum with an equal weight assigned to each stratum.

In particular, for Approach B the first three marks listed in Section 3.1 will be analyzed (IC50, IC80, IIP). The analyses of Approach B are consistently done in two ways: First, estimate and graph mark-specific prevention efficacy (with 95% CIs) for the VRC01 dose groups pooled vs. placebo. Second, estimate and graph mark-specific prevention efficacy (with 95% CIs) for the VRC01 lower dose vs. placebo in a left panel and the VRC01 higher dose vs. placebo in the right panel.

Additional details of Implementation of Approach B PH Phenotypic Sieve Analysis

We describe implementation details of the Sun and Gilbert (2012) / Gilbert and Sun (2015) method. The following README file describes the computer code for implementing the methods:

```
T:\vaccine\p704\analysis\efficacy\code\
NonparametricSmoothingPHsieveanalysisSunetal2015\
READMEcodeforimplementingApproachBPHforAMPfinalreporting.txt
```

The code implements the method 81 times (viewed as sensitivity analyses given the high correlation of the IC50, IC80, and IIP markers), based on the cross-classification of the following factors:

- For each of 704/085, 703/081, and 704/085+703/081 (3 cohorts);
- For each of the marks IC50, IC80, IIP listed in Section 3.1, defined in 3 possible ways: most-frequent synthesized variant, most sensitive variant, least sensitive variant (9 total neutralization resistance markers); and
- For the VRC01 treatment arms pooled and for VRC01 30 mcg/ml vs. placebo and for VRC01 10 mcg/ml vs. placebo (3 analyses).

For each application, the optimal bandwidth is selected using an analytic optimal bandwidth formula used in Sun et al. (2016) and Yang et al. (2017): bandwidth $h = C\sigma_{\text{sigmav}}no^{1/3}$ with C a constant, σ_{sigmav} is the estimated standard deviation of the observed marks, and no is the number of endpoint cases, which has been used in situations with a very large phase-one sample and low event rate (Yang et al., 2017). We implement the formula with $C = 5$ for IC50 and IC80 and $C = 6$ for IIP. In addition, we select the bandwidths for the analyses of VRC01 pooled versus placebo, and apply those selected bandwidths to the VRC01 higher dose vs. placebo and VRC01 lower dose vs. placebo analyses. The selected bandwidths are reported with the results of analyses. If the analyses do not produce stable results, then the constant C is increased until stable results are obtained; this occurred for the following analyses:

- 704/085 10 mcg/placebo (C adjusted to 8,8,9 for the three marks, respectively)
- 703/081 30 mcg/placebo (C adjusted to 8,8,9 for the three marks, respectively)
- 704/085 + 703/081 30 mcg/placebo (C adjusted to 8,8,9 for the three marks, respectively)

A small percentage of the disease cases have high IC50 and/or IC80 values, defined by values greater than 10 mcg/ml. The protocol defines a value > 10 mcg/ml as resistant. Therefore, before implementing the analyses, all IC50 values > 10 mcg/ml are set to 10 and all IC80 values > 10 mcg/ml are set to 10. This assures that outlying very resistant viruses do not have undue influence on the prevention efficacy curve estimation results. In addition, IIP values with $IC80 - IC50 \leq 0$ can be infinity depending on the concentration value used; infinity values are set to the maximum IIP value less than infinity.

The analysis is implemented with marks placed on a 0 to 1 scale, and for plotting the marks are transformed back to the original scale, for interpretability. Other parameters needed for implementation are set as follows (in the notation of Gilbert and Sun, 2015): $tband = 0.5$, $a_0 = 0.01$, $a_1 = 0.02$, $b_1 = 1.0$, a time grid of 100 equally spaced increments, and a mark grid on 100 equally spaced increments. The end of follow-up time is set the same as for the primary analyses of prevention efficacy.

For each analysis, the result is reported as point and 95% confidence interval estimates of prevention efficacy as a function of the mark IC50, IC80, and IIP with figures portraying the results. In

addition, the same results for IC50 and IC80 are reported again, except using a new x-axis scale to aid interpretability in terms of a potential serum neutralization titer correlate of prevention efficacy. In particular, IC50 for each case is replaced with the median participant-specific mid-point infusion visit concentration over the primary follow-up period divided by IC50, which is interpreted as the predicted serum ID_{50} against the founder virus in a hypothetical scenario that the exposures causing transmissions occur at mid-point infusion visits. The median mid-point concentration represents the ‘average’ / ‘central’ value of concentration at exposures to HIV-1 infection, given that exposures are expected to happen approximately uniformly over trial follow-up, such that these analyses can give clues about correlates. The median mid-point concentrations are calculated accounting for the proportion of cases that occur in the 10 and 30 mg/kg dose groups, and for the proportion of cases that occur in the 704/085 and 703/081 trials.

The hypothesis testing procedures of Gilbert and Sun (2015) are applied. First, the infimum test statistic $T_{m1}^{(1)}$ (notation in Gilbert and Sun 2015) is applied to test the null hypothesis $H_{10} : PE(v) = 0$ against the monotone alternative hypothesis H_{1m} that $PE(v) \geq v$ with strict inequality for at least one v . Second, the infimum test statistic $T_{m1}^{(2)}$ (notation in Gilbert and Sun 2015) applied to test the null hypothesis $H_{20} : PE(v) = PE$ against the monotone alternative H_{2m} that $PE(v)$ decreases as v increases. Importantly, because the neutralization resistance markers are highly correlated, results are anticipated to be similar across analyses, such that the analyses are viewed as sensitivity analyses, examining consistency of results across slightly different ways to define neutralization resistance markers, and multiplicity adjustment of p-values is not done.

The semiparametric proportional hazards estimation and hypothesis testing methods of Juraska and Gilbert (2013) are applied for the same 81 analyses listed above. No bandwidths are used for these analyses. First, the one-sided weighted Wald test of $\{H_{10} : PE(v) = 0 \text{ for all } v\}$ is applied: for IC50 and IC80, the test statistic in formula (11) in Juraska and Gilbert (2013) is used, designed to increase power to detect alternatives where both the marginal $PE > 0$ and $PE(v)$ decreases with v ; for IIP, the test statistic in formula (11) with the $-$ signs replaced with the $+$ signs is used, designed to increase power to detect alternatives where both the marginal $PE > 0$ and $PE(v)$ increases with v . Second, the one-sided Wald test of $\{H_{20} : PE(v) = PE \text{ for all } v\}$ is applied: for IC50 and IC80, the Wald test statistic (Juraska and Gilbert, 2013, Section 3) for the mark coefficient in the density ratio model is used to test H_{20} against $\{H_{21} : PE(v) \text{ decreases with } v\}$; for IIP, the same Wald test statistic is used to test H_{20} against $\{H_{22} : PE(v) \text{ increases with } v\}$.

3.3 Multiple hypothesis testing adjustment for phenotypic/neutralization sieve analysis

As noted above, no adjustments for multiple hypothesis testing for neutralization sieve analysis are done, for the following reason. The nine quantitative neutralization marks defined by IC50, IC80, and IIP cross-classified by (most frequent, most sensitive, least sensitive) variant have a high degree of positive correlation (reported in the manuscript), such that it is more useful to think of the analyses of the different marks as sensitivity analyses, and to examine the consistency of the p-values across the analyses. In addition, use of the multiple hypothesis testing methods (Gilbert and Sun (2015) and Juraska and Gilbert (2013) for Approach B, and cumulative incidence analysis of ordered categorical neutralization types) is viewed as another layer of sensitivity analysis. Note

that p-values are not computed for neutralization sieve analysis Approach A.

4 Analysis of VRC01 vs. Placebo Effect on Viral Load at First HIV-1 RNA PCR Positive Time point

The viral load measured at the first HIV-1 RNA PCR positive time point in primary endpoint cases was analyzed using the same method as used for Approach A neutralization sieve analysis – DRTMLE. Specifically, DRTMLE with the same models and covariate adjustment was employed to estimate the geometric mean viral load in each randomization arm with a 95% confidence interval, and to obtain a point estimate and 95% confidence interval for the ratio of geometric mean viral loads (VRC01 pooled / placebo), as well as a two-sided Wald p-value for testing whether this ratio of geometric means departed from one.

Given the hypothesis that VRC01 may only suppress viral load if the acquired virus is sensitive to neutralization by VRC01, the analysis was repeated restricting to in vitro sensitive viruses (defined by least sensitive variant $IC_{80} < 1 \mu g/ml$), and for the complement set of viruses (with least sensitive variant $IC_{80} \geq 1 \mu g/ml$). Because of the small sample size of infected participants with virus $IC_{80} < 1 \mu g/ml$, the modeling and covariate-adjustment through DRTMLE was not supported by the data. Therefore, covariate-unadjusted analysis of these in vitro sensitive viruses was done, where the geometric mean viral load for each randomization arm was estimated by the sample geometric mean with 95% confidence interval computed using the t-distribution. Similarly the t-distribution was used to produce a 95% confidence interval about the ratio of geometric mean viral loads (VRC01 pooled / placebo). The Wilcoxon rank sum test was used to test whether the distribution of viral load differed for VRC01 pooled vs. placebo.

References

- Benkeser, D., Carone, M., Laan, M. V. D., and Gilbert, P. (2017), “Doubly robust nonparametric inference on the average treatment effect,” *Biometrika*, 104, 863–880.
- Gilbert, P., Wang, M., Wrin, T., Petropoulos, C., Gurwith, M., Sinangil, F., D’Souza, P., Rodriguez-Chavez, I. R., DeCamp, A., Giganti, M., et al. (2010), “Magnitude and breadth of a nonprotective neutralizing antibody response in an efficacy trial of a candidate HIV-1 gp120 vaccine,” *Journal of Infectious Diseases*, 202, 595–605.
- Gilbert, P. and Y, S. (2015), “Inferences on relative failure rates in stratified mark-specific proportional hazards models with missing marks, with application to human immunodeficiency virus vaccine efficacy trials.” *Journal of the Royal Statistical Society: Series C (Applied Statistics)*., 64, 49–73.
- Juraska, M. and Gilbert, P. (2013), “Mark-specific hazard ratio model with multivariate continuous marks: An application to vaccine efficacy.” *Biometrics*, 69, 328–337.
- (2016), “Mark-specific hazard ratio model with missing multivariate marks.” *Lifetime Data Analysis*., 22, 606–625.
- Lunn, M. and McNeil, D. (1995), “Applying Cox regression to competing risks.” *Biometrics*, 51, 524–532.
- Montefiori, D. (2014), “Importance of neutralization sieve analyses when seeking correlates of HIV-1 vaccine efficacy.” *Human Vaccine Immunotherapy*, 10(8), 2507–2511.
- Shepherd, B., Gilbert, P., Jemai, Y., and Rotnitzky, A. (2006), “Sensitivity analyses comparing outcomes only existing in a subset selected post-randomization, conditional on covariates, with application to HIV vaccine trials.” *Biometrics*, 62, 332–342.
- Sun, Y. and Gilbert, P. (2012), “Estimation of stratified mark-specific proportional hazards models with missing marks.” *Scandinavian Journal of Statistics*, 39, 34–52, pMCID: PMC3601495.
- Sun, Y., Gilbert, P., and McKeague, I. (2009), “Proportional hazards models with continuous marks.” *Annals of Statistics*, 37, 394–426, pMCID: PMC2762218.
- Sun, Y., Li, M., and Gilbert, P. (2016), “Goodness-of-fit test of the stratified mark-specific proportional hazards model with continuous mark.” *Computational Statistics and Data Analysis*, 93, 348–358, pMCID: PMC4598956.
- Yang, G., Sun, Y., Qi, L., and Gilbert, P. (2017), “Estimation of Stratified Mark-Specific Proportional Hazards Models Under Two-Phase Sampling with Application to HIV Vaccine Efficacy Trials.” *Statistical Biosciences*, 9, 259–283.

Amendments made to the Statistical Analysis Plan

Version 1 (21 October 2016) sent to DSMB prior to November 2016 DSMB meeting

Version 1.1 (9 February 2017)

* Minor changes to the Feasibility Check Section 9.1 to simplify the definitions of discontinued participation.

Version 1.2 (6 July 2017)

Section 9.4 and its subsections have been rewritten to describe a revised monitoring plan for futility to assess PE. The revised plan facilitates futility assessment by the DSMB and provides better guidance to decisions concerning trial conduct, taking into account the trial's proof-of-concept design. The revised language also reflects requests from the DSMB, expressed at a meeting held April 26, 2017, regarding the scope of interim futility analyses. The revised plan focuses on estimating the distribution of the number of HIV-1 infection endpoints by Week 80 rather than (previously) on the distribution of time to a prespecified number of endpoints. Futility guidelines are defined in terms of probabilities of reaching prespecified targets for the number of endpoint infections. Targets monitored for include inability to achieve the planned 90% power and inability to achieve 50% power for PE = 60%.

Version 1.3 (3 April 2018)

A minor revision concerning the content and timing of the treatment-blinded futility report in Section 9.4. Version 1.3 states that estimates based on treatment-blinded data in scenarios (i)-(iii), i.e., including the observed pooled incidence rate scenario, will be reported. Version 1.3 also states that the treatment-blinded report will be shared with the Leadership Group before (rather than after) each DSMB meeting takes place. In addition, in Section 9.4.2.1, the sample size in HVTN 703/HPTN 081 has been updated to N=1900 (from 1500), and the estimated total person-time at risk in this trial has been updated accordingly.

Version 1.4 (13 June 2018) (mis-labeled Version 1.5)

In Section 8.1, the definition of the time-to-event variable in the primary PE analysis has been revised as the time since enrollment rather than since randomization.

Version 1.5 (21 July 2018)

In Section 9.2.2, the operational definition of the latest timepoint t at which estimation and inference about $PE(t)$ is performed has been revised to account for instability of the estimator at the cumulative incidence scale. It has also been added that this timepoint t will be chosen in DSMB reports for determining whether a stopping boundary is crossed or not. Also, in Section 9.2.2, added the following sentence to be clear that the boundary was defined in Table 3: As stated in Table 3, the non-efficacy stopping boundary is defined by the 2-sided upper 95% confidence limit for PE being at 40%, where the 95% CI lying below 40% constitutes meeting the guideline for non-efficacy.

Version 1.6 (30 July 2018)

- Added Section 7.1.2.1 on the analysis of infusion reactions.
- Added Section 9.2.2.2 on some additional analyses that are presented in DSMB reports on prevention efficacy by neutralization sensitivity.
- On page 13 of the SAP, removed "In addition" from the sentence beginning "In addition, if there are more than 10 HIV infection events in each of the VRC01 dose groups to clarify that this is the only primary analysis that will occur under those conditions.
- On page 28 of the SAP, made clarifications in the paragraph beginning "At each non-efficacy interim analysis PE is estimated with a 2-sided 95% nominal confidence interval" including adding the sentence "Cumulative prevention efficacy through time t , $SPE(t)$, will be estimated with fixed time point t

chosen to be the latest possible time point within the Week 80 visit window (or earlier if necessary) where stable estimation can be achieved; this is operationalized by defining t_t as the maximum time point with available follow-up data from 150 participants in each of the placebo and pooled VRC01 groups."

- Modified the last paragraph of Section 9.2 to be clear that individual VRC01 treatment arm comparisons are also included in interim monitoring reports for which non-efficacy is evaluated.

Version 1.7 (5 September 2018)

Section 1

- Modified the sample size of AMP HVTN 702/HPTN 081 to reflect the change that had been approved (now 1900 instead of 1500).
- Added the statement that the enrollment period of each AMP trial completes on September 30, 2018.

Section 4

- Clarified that "Analyses of correlates of prevention efficacy are based on participants in cohorts defined in the Correlates of Prevention Efficacy SAP" and revised the Correlates of Prevention Efficacy SAP to define the cohorts used for the correlates analyses.

Section 8

- In Section 8.1., added a description of how all of the primary and secondary analyses of prevention efficacy will be done both for each AMP trial separately and pooling over the two AMP trials, with details on how the pooled analyses are done.
- In Section 8.1, clarified how secondary as-treated analyses will be done in the Per-Protocol cohort.
- Section 8.1 has been updated to include the operational rule for determining the time point t at which inference about the primary efficacy estimand, $PE(t)$, will be conducted. In addition, operational rules for right-censoring of times-to-event at the Week 80 visit have been added in Table 1.
- In Section 8.2, clarified the baseline demographic variables that are adjusted for in secondary analyses of prevention efficacy.
- Added a section 8.2.1 to state that the primary analyses of prevention efficacy and the Cox model secondary analyses of prevention efficacy will be repeated including HIV-1 infections through to the Week 104 terminal study visit.
- Added Section 8.3 describing key secondary analyses of prevention efficacy against viruses measured to be sensitive to neutralization by VRC01. The previous SAP specified some of these analyses in the interim monitoring section, such that this change clarifies that these analyses are also included in the final analysis report.

Section 9

- Section 9.2.2 has been revised to match the updated text in Section 8.1.

- In Section 9.2.2, deleted the following paragraph describing the interim analysis, which was incorrect: "In all interim analyses of PE, participants with either event of CRF-confirmed study termination prior to study completion or 20 consecutive weeks without participant contact are right-censored at the time of occurrence of the first of these events. Twenty consecutive weeks represents two consecutive planned infusions, with 4 weeks of margin for variability in infusion visit windows."

Version 1.8 (April 17, 2019)

- In Section 9.2.2, added the sentence: "In addition, a supplemental analysis will estimate the proportional-hazards PE parameter (defined in \eqref{HR PE definition}) with a 2-sided 95% confidence

interval and a two-sided p-value for whether proportional-hazards PE differs from unity, following the same statistical procedures described for the final analysis plan (see Section 8.2)."

Version 1.9 (August 7, 2019)

Added the following text to the end of Section 8.1:

"The same method will be applied to obtain an estimate of cumulative PE on the additive difference-scale (pooled VRC01 group minus control group) with pointwise and 95% confidence intervals. This analysis is informative because it communicates about benefits and risk on an absolute scale: for example under the assumption that assignment to a VRC01 arm does not increase the risk of infection for any participant, the estimate at a given time t is interpreted as the probability a participant assigned to a VRC01 arm has their infection averted compared to, counter to fact, had they been assigned to placebo."

Added the following text to Section 8.2:

"TMLE analyses will produce plots of estimated cumulative PE on both the multiplicative vaccine efficacy and additive-difference scales, as done for the primary analyses. The TMLE analyses will be implemented using the *survtmle* R package available at CRAN."

Incorporated additional details about the primary estimation procedure in Sections 8 and 8.1. The passage in Section 8

"The statistical methods are the same, except the pooled analyses adjust for study. For cumulative incidence based analyses this adjustment is made by estimating cumulative incidence separately within country (requiring at least 10 total primary HIV-1 infection endpoints), and for Cox model based analyses this adjustment is made by using a separate baseline hazard for each country (again requiring at least 10 total primary HIV-1 infection endpoints within a country to include the trial as a distinct covariate level)."

has been revised as

"The statistical methods are the same, except the pooled analyses additionally stratify/adjust for study. For cumulative incidence based analyses the stratification is performed by estimating the cumulative hazard separately within each combination of study and VRC01 dose group (requiring at least 10 total primary HIV-1 infection endpoints within each combination of study and VRC01 dose group), and for Cox model based analyses this adjustment is made by using a separate baseline hazard for each study (requiring at least 10 total primary HIV-1 infection endpoints within each study to include the trial as a stratification covariate)."

and the passage in Section 8.1

"If there are more than 10 HIV infection events in each of the VRC01 dose groups, then the above estimators will be computed separately for each dose group and aggregated for inference on PE."

has been revised as

"If there are more than 10 HIV-1 primary endpoints in each of the VRC01 dose groups, then the Nelson-Aalen estimator for the cumulative hazard function will be computed separately for each dose group and the weighted average of the dose group-specific estimates, with the weight 0.5 assigned to each dose group, will be transformed for inference about PE. The variance estimate of the overall averaged

cumulative hazard estimator will be used to obtain the variance estimate on the log cumulative incidence ratio scale for calculating confidence intervals. For trial-pooled analyses, if there are more than 10 primary endpoints in each stratum defined by trial and VRC01 dose group, the Nelson-Aalen estimator will be computed separately in each of the 4 strata and the weighted average of the stratum-specific estimates, with weights 0.25 assigned to each stratum, will be transformed for inference about the trial-pooled PE."

Version 2.0 (August 28, 2019)

In Section 3, the following paragraph was added to address duplicate enrollments:

"In the unexpected event of a duplicate enrollment, the interim safety and infusion discontinuation data will be reported for each enrollment, considering these as separate participants, while noting in the report that a duplicate enrollment occurred. The final safety report will include only the safety and infusion discontinuation data following the first randomization, analyzed according to the randomized treatment assignment. The immunogenicity and prevention efficacy analyses will also use the data from the first randomization (e.g., the earliest enrollment time will be used to determine the participant's follow-up time)."

In Section 8, to address stratification in the control group, the passage

"For cumulative incidence based analyses the stratification is performed by estimating the cumulative hazard separately within each combination of study and VRC01 dose group (requiring at least 10 total primary HIV-1 infection endpoints within each combination of study and VRC01 dose group), and for Cox model based analyses the stratification is performed by using a separate baseline hazard for each study (requiring at least 10 total primary HIV-1 infection endpoints within each study to include the trial as a stratification covariate)."

has been revised as

"For cumulative incidence-based pooled analyses, stratification is performed by estimating the cumulative hazard separately within each combination of study and treatment group (requiring at least 10 total primary HIV-1 infection endpoints within each combination of study and treatment group), and, for Cox model-based pooled analyses, stratification is performed by using a separate baseline hazard for each study (requiring at least 10 total primary HIV-1 infection endpoints within each study to include the trial as a stratification covariate)."

and, in Section 8.1, to address stratification in the control group, the passage

"For trial-pooled analyses, if there are more than 10 primary endpoints in each stratum defined by trial and VRC01 dose group, the Nelson-Aalen estimator will be computed separately in each of the 4 strata and the weighted average of the stratum-specific estimates, with weights 0.25 assigned to each stratum, will be transformed for inference about the trial-pooled PE."

has been revised as

"For trial-pooled analyses, if there are more than 10 primary endpoints in each stratum defined by trial and treatment group, the Nelson-Aalen estimator will be computed separately in each of the 6 strata (4 VRC01 dose group strata and 2 control group strata), and separate weighted averages of the VRC01 dose-group and control-group stratum-specific estimates, with weights 0.25 assigned to each VRC01 dose-

group stratum and weights 0.5 assigned to each control-group stratum, will be transformed for inference about the trial-pooled PE."

Version 3.0 (October 18, 2019)

Revised the definition of the PP cohort in Section 4 for increased clarity.

Revised Table 1 to account for interim visits.

Added the following clarification statement concerning the primary analysis timepoint t:

"Note that the fixed time point t will likely differ for the two AMP trials given the dynamic visit windows. By definition of the stratified estimator, the trial-pooled analysis will use the smaller of the two fixed time points t."

Added the following implication of the operational rules set in Table 1:

"Additionally, note that, due to differences between Schedules 1 and 4, the operational rules in Table 1 imply that an infection endpoint observed in Schedule 4 after the hypothetical Schedule 4 Week 80 visit would be excluded from primary endpoints, while an infection endpoint observed in Schedule 1 at the same time post-enrollment would be included as a primary endpoint if the endpoint was registered before or at the Schedule 1 Week 80 visit."

Revised the description of a secondary efficacy analysis in Section 8.2 as follows:

"An additional secondary analysis of PE based on the Cox proportional hazards model will be done that uses as the failure time variable the time from the most recent infusion to the estimated date of HIV-1 infection."

Deleted the phrase "which is a conservative approach to estimation of PE by sensitivity type" in the following statement in Section 8.3.1:

"For infected cases with multiple assayed HIV-1 variants, the geometric mean IC50 and IC80 pertaining to the most sensitive variant is used for analysis, which is a conservative approach to estimation of PE by sensitivity type."

Added the definition of the founder virus in Section 8.3.1:

"A 'founder virus' is an HIV-1 variant that is measured/observed based on sequencing the earliest available post-infection sample."

In Section 8.5, the statement

"In addition, if there is substantial PrEP use detected over the course of the study, then a Cox model with PrEP detectability as a time-varying covariate will be used to assess different prevention efficacy by time-varying subgroup and for each subgroup separately."

has been revised as

"In addition, if there is substantial PrEP use detected over the course of the study, then a marginal structural Cox model will be used to assess prevention efficacy in the sub-population not using PrEP."

In Section 8, the statement about the timing of the final analysis

"The final prevention efficacy analysis will occur when the last enrolled participant has reached the Week 88 visit."

has been revised as

"Unless either of the trials is stopped prematurely, the common data cut date for the final prevention efficacy analysis in both trials is set to be May 1, 2020, which includes more than 80 weeks of follow-up for the last enrolled participant in each trial (80 weeks after the last enrollment falls on April 2, 2020 in HVTN 703/HPTN 081 and April 17, 2020 in HVTN 704/HPTN 085)."

Version 3.1 (December 11, 2019)

In Section 4, the handling of duplicate enrollments in final immunogenicity and efficacy analyses, previously described as

"The immunogenicity and prevention efficacy analyses will also use the data from the first randomization (e.g., the earliest enrollment time will be used to determine the participant's follow-up time)."

has been revised as

"The immunogenicity and prevention efficacy analyses will exclude all data from participants with a duplicate enrollment regardless of whether also duplicate randomization occurred or not."

Version 3.2 (February 28, 2020)

Section 8.6 describing the construction of the HIV-1 risk predictor has been fully updated.

In Section 4, the definition of the MITT cohort

"participants in the Safety Cohort who are not later discovered to have been HIV-infected on the date of the first infusion (Day 0)"

has been revised as

"participants in the Safety Cohort who are not later discovered to have been HIV-infected on the date of the first infusion (Day 0) and who are not involved in a duplicate enrollment".

In Section 5.3, the statement

"The date of HIV-1 infection diagnosis will be used as the event-date for primary time-to-event analyses of Primary Endpoint (documented HIV-1 infection)."

has been revised as

"The date of HIV-1 infection diagnosis will be used as the event-date for primary time-to-event analyses of Primary Endpoint~2 (documented HIV-1 infection) and for all secondary time-to-event analyses of Primary Endpoint 2 that analyze time since enrollment as the failure time variable."

The Section 5.4 heading

"Estimated Date of HIV-1 Infection via the 'Look-Back' Procedure for HIV-Specific PCR Testing"

has been revised as

"Estimated Date of HIV-1 Infection".

In addition, the Section 5.4 paragraph

"For all participants diagnosed with HIV-1 infection, the sample available at the nearest date before the diagnosis date will be tested using HIV-specific PCR. If it is positive, then the sample at the second nearest date before the diagnosis date will be tested using HIV-specific PCR. This 'look-back' procedure will be repeated until an HIV-specific PCR negative test result is obtained or until a test is done for a Day 0 sample. The default estimate of the date of infection is the midpoint between the last negative and the first positive PCR test result. The estimated infection date may be used as the event-date for marker correlates and sieve analyses of breakthrough HIV-1 infections (see the Correlates of Prevention Efficacy SAP for details) and may also be used for exploratory analyses of the primary efficacy endpoint. The estimator of the date of HIV-1 infection may be refined to be based on additional data beyond the diagnostic testing information (details of this estimator are described in the Correlates of Prevention Efficacy SAP)."

has been revised as (new text is underlined)

"For all participants diagnosed with HIV-1 infection, the sample available at the nearest date before the diagnosis date will be tested using HIV-specific PCR. If it is positive, then the sample at the second nearest date before the diagnosis date will be tested using HIV-specific PCR. This 'look-back' procedure will be repeated until an HIV-specific PCR negative test result is obtained or until a test is done for a Day 0 sample. The complete HIV diagnostic test history including retrospective testing is used to estimate the date of infection as described in detail in Section 4.2 of the Correlates of Prevention Efficacy SAP. The estimated infection date will be used as the event-date for secondary analyses of Primary Endpoint 2 that analyze time since last infusion received prior to the estimated infection date as well as for marker correlates and sieve analyses of breakthrough HIV-1 infections (see the Correlates of Prevention Efficacy SAP for details) and may also be used for exploratory analyses of the primary efficacy endpoint. The estimator of the date of HIV-1 infection may be refined to be based on additional data beyond the diagnostic testing information (details of this estimator are described in the Correlates of Prevention Efficacy SAP)."

In Section 8.1, a typo (underlined text) in the statement

"...defining t as the maximum time point with 150 participants at risk for the primary endpoint in each of the placebo and pooled VRC01 groups"

has been revised as

"...defining t as the maximum time point with 150 participants at risk for the primary endpoint in each of the placebo and individual VRC01 groups."

In Section 8.1, the statement

"The same method will be applied to obtain an estimate of cumulative PE on the additive difference-scale (pooled VRC01 group minus control group) with pointwise and 95% confidence intervals."

has been revised as

"The same method will be applied to obtain an estimate of cumulative PE on the additive difference-scale (control group minus pooled VRC01 group) with pointwise and simultaneous 95% confidence intervals."

In Section 8.2, the statement

"This analysis is conducted in an as-treated fashion in the PP cohort as described in the previous paragraph."

has been revised as

"This analysis is conducted in the MITT cohort."

In Section 8.2, the statement

"The Cox model will also be used for a secondary analysis to assess PE in the PP cohort by modeling full cumulative infusion adherence (i.e., at study time t , all infusions up to and including time t received within target visit windows) or lack thereof as a binary time-varying covariate."

has been revised as

"The Cox model may also be used for a secondary analysis to assess PE in the MITT cohort by modeling full cumulative infusion adherence (i.e., at study time t , all infusions up to and including time t received within target visit windows) or lack thereof as a binary time-varying covariate."

In Section 8.2, the statement

"In addition, the primary analysis of prevention efficacy will be repeated, again using the same code except that participants are right-censored by the event of no longer qualifying for membership in the PP cohort."

has been deleted.

In Section 8, the data cut date for the primary analyses has been revised from May 1, 2020 to April 3, 2020. The reason for this revision was that the COVID-19 pandemic was about to start causing disruptions to trial operations, and an earlier data cut date aimed to preserve data quality for the primary analyses. As of March 27, 2020, 54 infusions remained to be administered in both AMP studies, representing a very small fraction of the over 40,000 infusions that have been completed.

Amendments to the Correlates of Prevention Efficacy SAP ("Marker SAP")

Section 2 of the Marker SAP summarizes the scope of statistical analyses designed to meet Secondary Objective 1 of the protocol. This scope includes (1) neutralization/phenotypic sieve analysis, (2) genetic/amino acid sequence sieve analysis, and (3) case-control correlates analyses for how VRC01 concentration and predicted serum neutralization titers to panels of virus isolates associate with instantaneous risk of HIV-1 infection. The original SAP included a specification for all of these analyses. However, as of October 2020 the data sets are not yet available/fully generated for analysis types (2) and (3) above, and moreover it was decided that these analyses should be reported in future publications, given that the scope of the current manuscript is the reporting of overall prevention efficacy results and neutralization sieve analysis results (1), which the authors think is the most appropriate scope for the primary study publication. In July of 2020, the Marker SAP was shortened to only include a description of the analyses for (1), while still retaining a summary of the broader scope of analyses as Section 2. The Marker SAP added the plan to analyze the VRC01 vs. placebo effect on viral load at first detection of HIV-1 infection in August of 2020.