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

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Division of AIDS (DAIDS)
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STUDY PRODUCT(S) PROVIDED BY

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Bethesda, Maryland, USA

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Contents

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

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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.

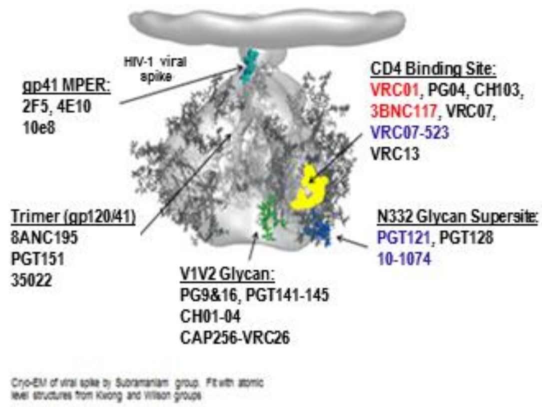


Figure 2-1 Neutralizing antibody epitopes on native Env timer

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

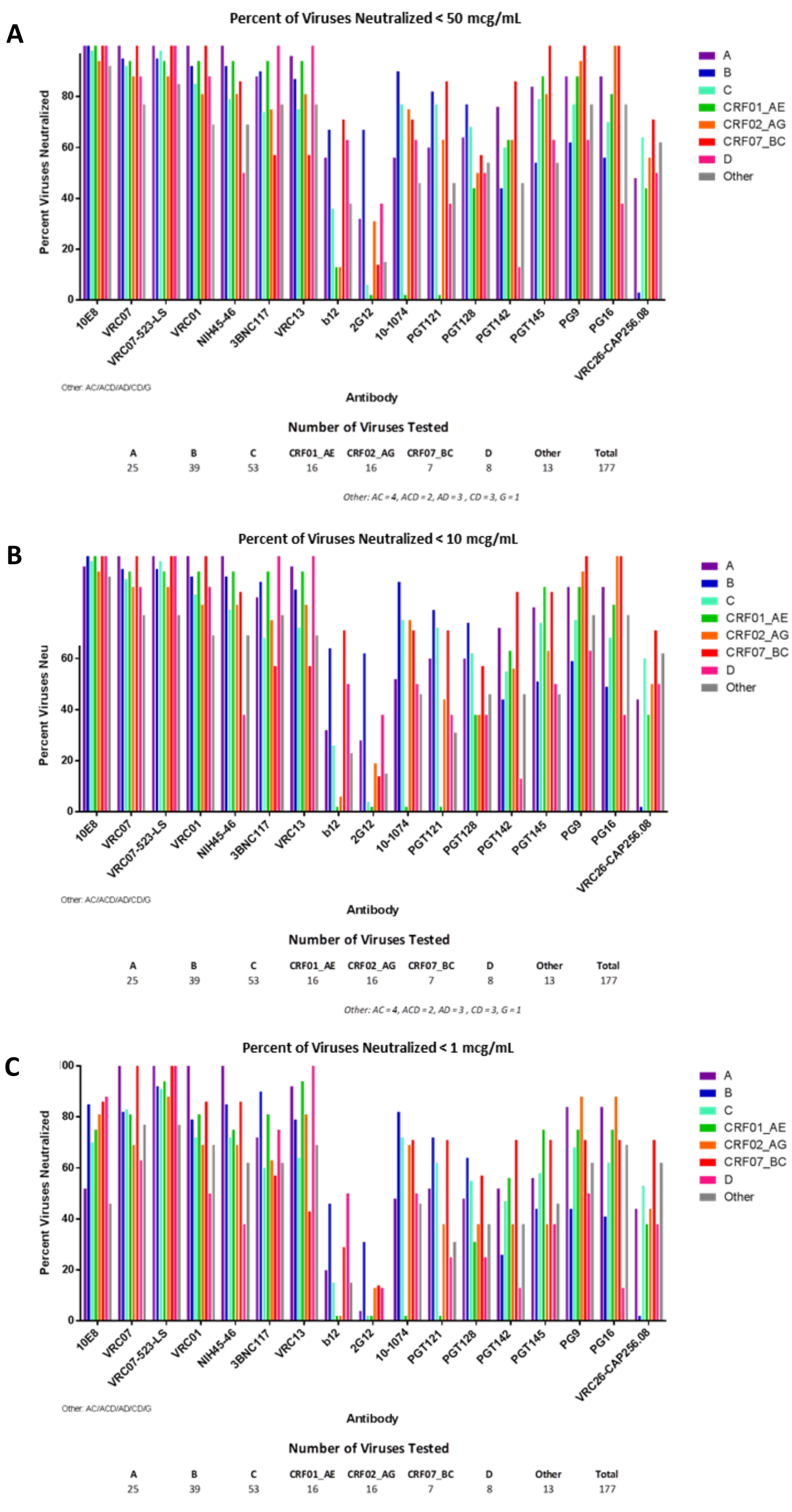


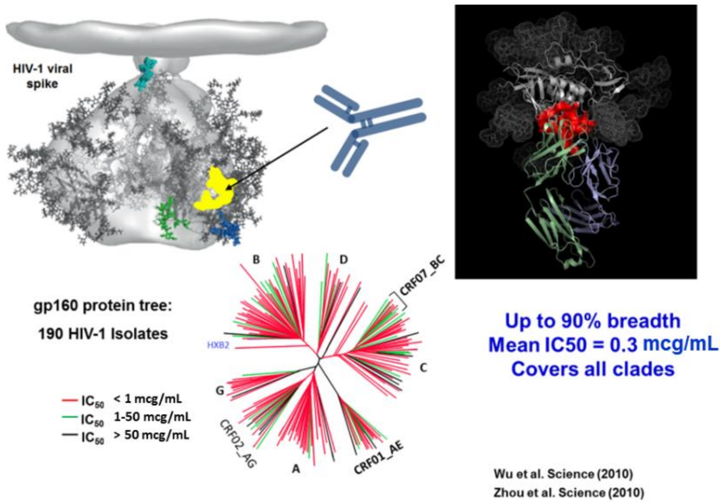
Figure 2-2 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL [31,48,53-56].

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 vialed 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	IC50 < 1 mcg/mL
A	22	100%	100%	95%
B	49	96%	94%	80%
C	38	87%	84%	66%
D	8	88%	88%	50%
CrRF01_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.

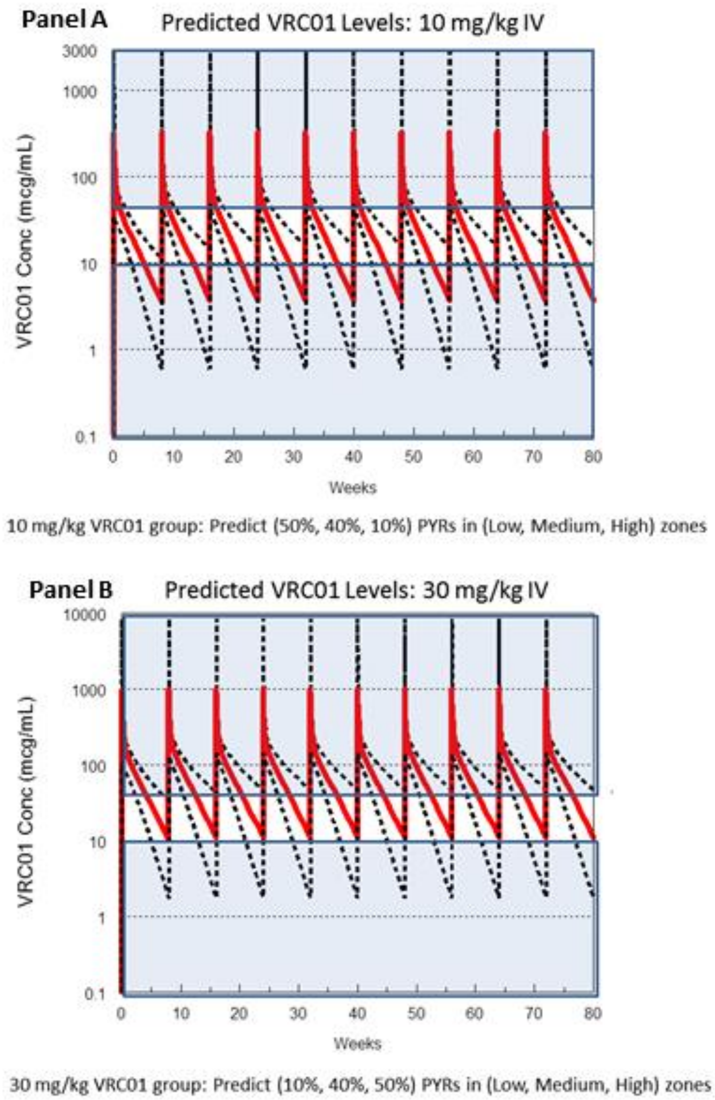
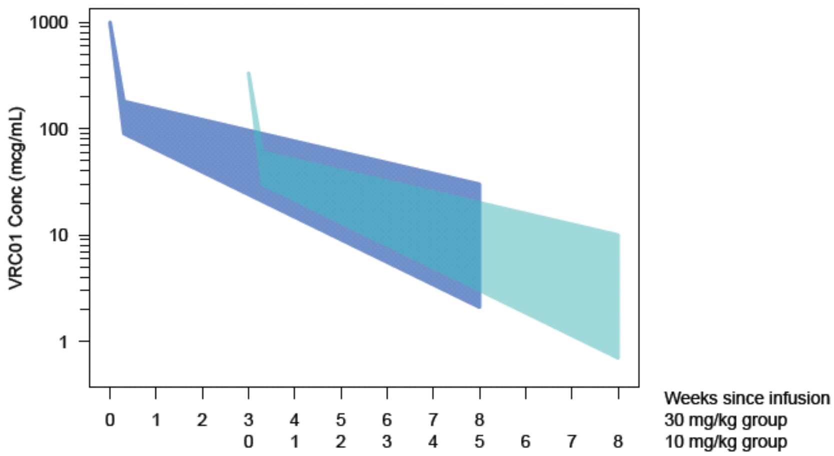


Figure 2-4 Predicted VRC01 serum concentrations over time. Panel A: Predicted VRC01 median serum concentration over time (solid lines) for 10 mg/kg IV infusions of VRC01 at Weeks 0, 8, 16, 24, 32, 40, 48, 56, 64, 72, with 95% confidence intervals (CI) (dashed lines). The shaded regions classify the serum 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.



	10 mg/kg	30 mg/kg	Overlap
High (> 50 mcg/mL)	10% PYRs	50% PYRs	**10% PYRs**
Medium (10 to 50 mcg/mL)	40% PYRs	40% PYRs	**40% PYRs**
Low (< 10 mcg/mL)	50% PYRs	10 % PYRs	**10 % PYRs**
		Total overlap = 60% PYRs	

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 ≥ 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 andit 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

*$TCID_{50}$ = 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 (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 2-6.

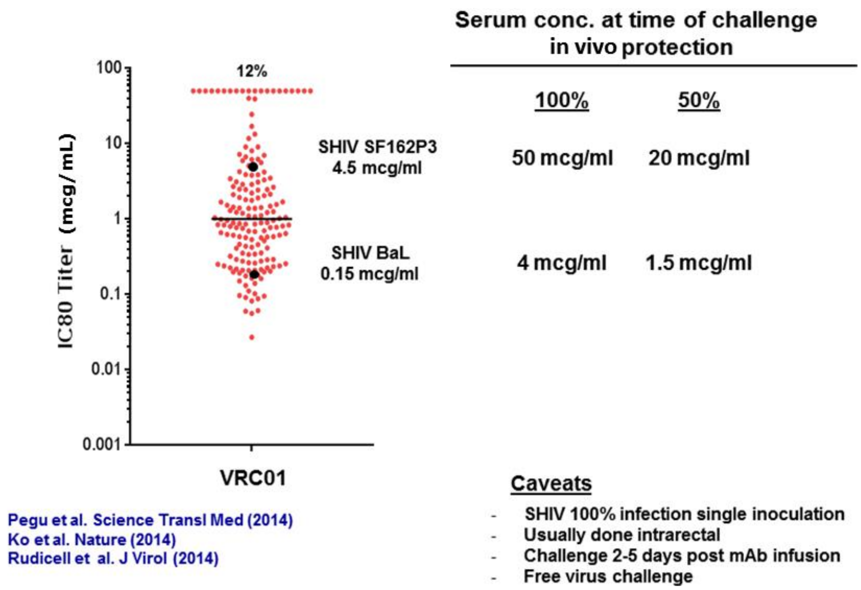


Figure 2-6 VRC01 IC_{80} values (170 Isolates) and serum concentrations in NHP SHIV challenge studies

It is particularly interesting to note that following administration of VRC01 to NHP, the antibody is found in mucosal tissues (see Figure 2-7), 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).

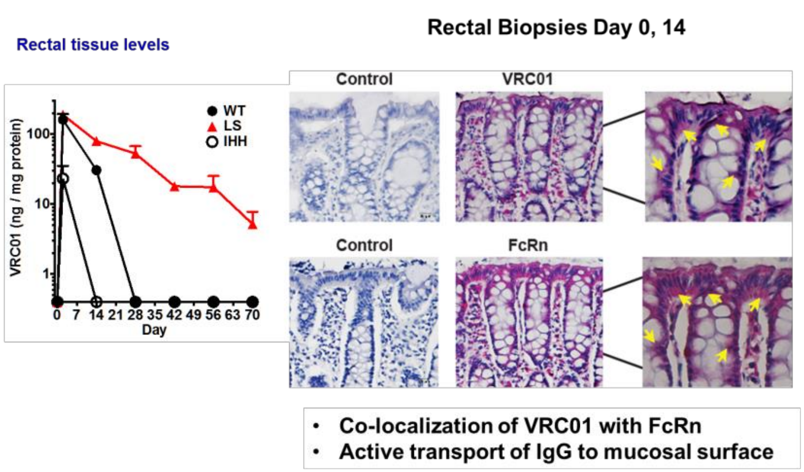


Figure 2-7 VRC01 mucosal pharmacokinetics in rhesus macaques [47]

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 ≥ 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 ≥ 0.5 log10 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-idiotype 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 – Cumul. incid. ratio (pooled mAb grp/control) of HIV-1 Dx by 80 Wks] × 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

> H0: PE $\leq$ 0% versus the alternative hypothesis H1: 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

PE10 = [1 – Cumul. incid. ratio (mAb-10 mg/kg grp/control) of HIV-1 Dx by 80 Wks] ×100%

and

PE30 = [1 – Cumul. incid. ratio (mAb-30 mg/kg grp/control) of HIV-1 Dx by 80 Wks] ×100%.

Within each cohort separately, secondary analyses test the null hypotheses

H0: PE10 $\leq$ 0% versus the alternative hypothesis H1: PE10 > 0%

and

H0: PE30 $\leq$ 0% versus the alternative hypothesis H1: 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 $\leq$ PE10 $\leq$ 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

H0: PE $\leq$ 0% versus the alternative hypothesis H1: 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) ≤ 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 H0: PE ≤ 0% in favor of H1: 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 H0: PE ≤ 0% in favor of H1: PE > 0% for different values of PE = PE10 = PE30 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%.

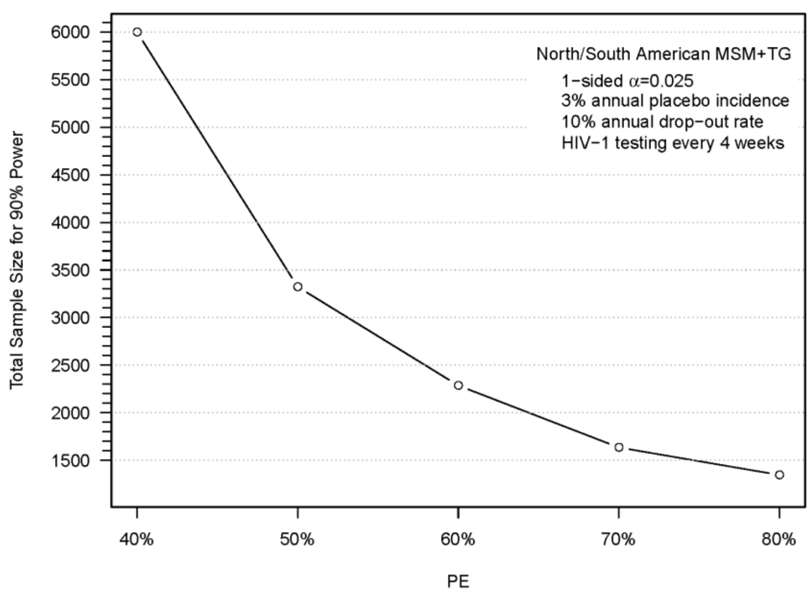


Figure 4-1 For the North/South American MSM + TG cohort, the total sample size for 90% power to reject H0: PE ≤ 0% in favor of H1: PE > 0% in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

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%

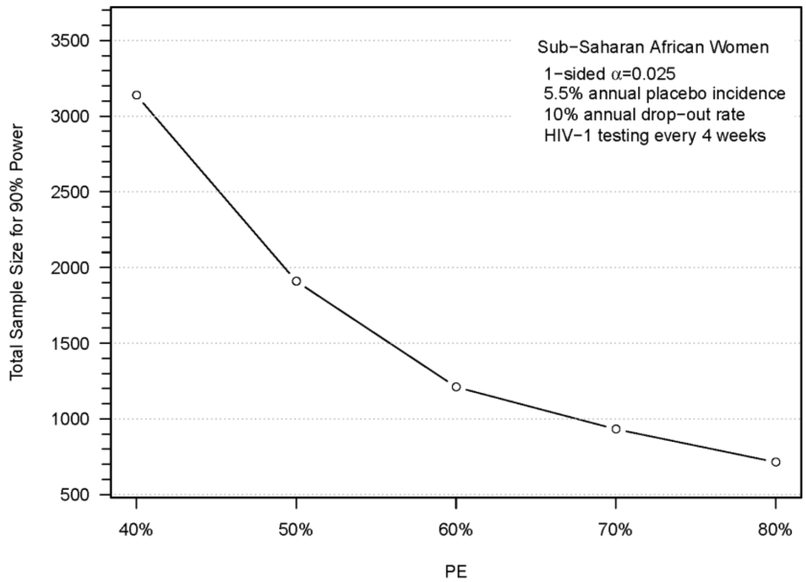


Figure 4-2 For the sub-Saharan African women cohort, the total sample size for 90% power to reject H0: PE ≤ 0% in favor of H1: PE > 0% in a 1:1:1 allocation design with 80 weeks of follow-up for HIV-1 infection for each trial participant

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 H0: PE ≤ 0% in favor of H1: PE > 0% for each of the two cohorts under different effect sizes PE = PE10 = PE30

	Unconditional Power (× 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 H0: PE ≤ 0% in favor of H0: PE > 0% for a range of fixed values of the pooled PE. The power for rejecting H0 when the HIV-1 incidence rate is lower than projected or dropout rate is higher than projected are included in each figure.

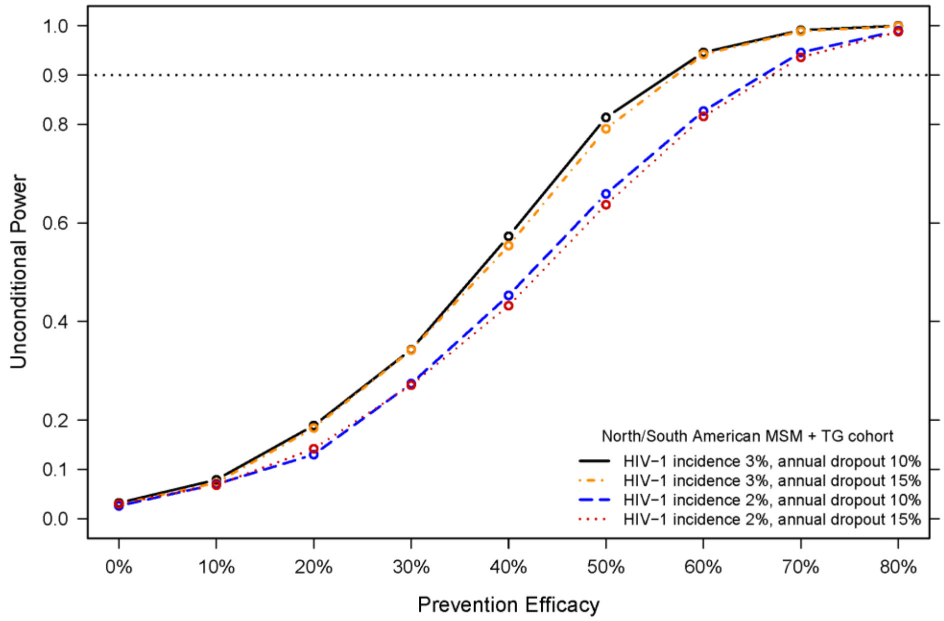


Figure 4-3 For the North/South American MSM + TG cohort and pooled mAb treatments, the power for rejecting H0: PE ≤ 0% in favor of pooled prevention efficacy of level PE based on primary assumptions for HIV-1 incidence rate and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

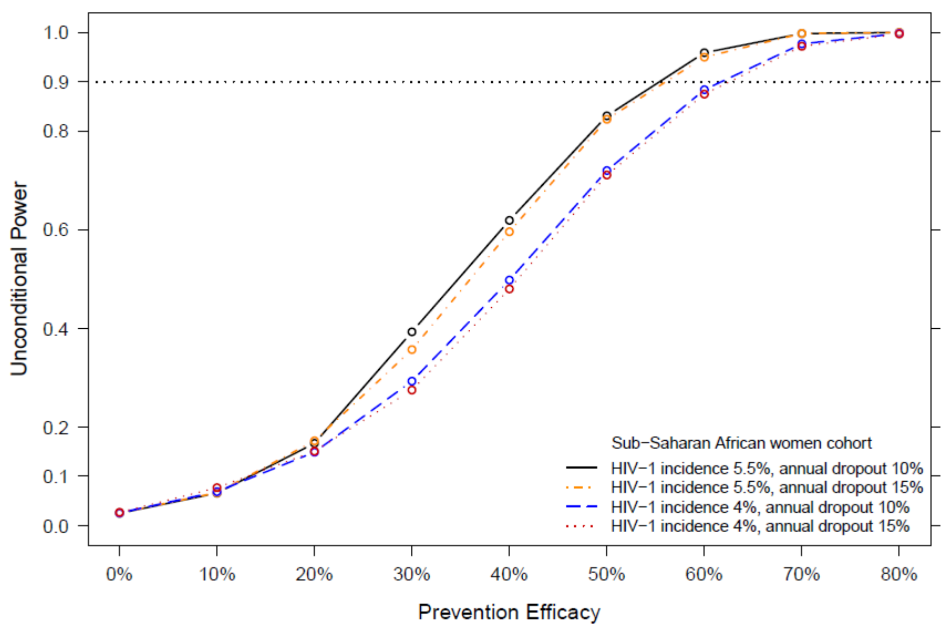


Figure 4-4 For the sub-Saharan African women cohort and pooled mAb treatments, the power for rejecting H0: PE ≤ 0% in favor of pooled prevention efficacy of level PE based on primary assumptions for HIV-1 incidence rate and dropout rate. Power curves are also shown for a lower than expected HIV-1 incidence 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 H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%.

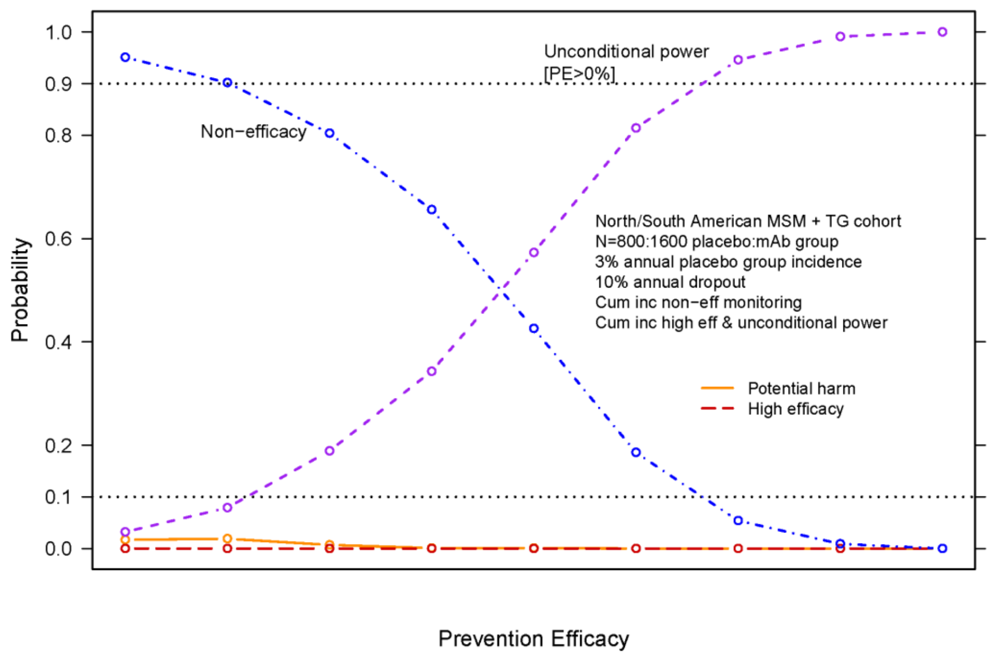


Figure 4-5 [North/South American MSM + TG cohort] Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups

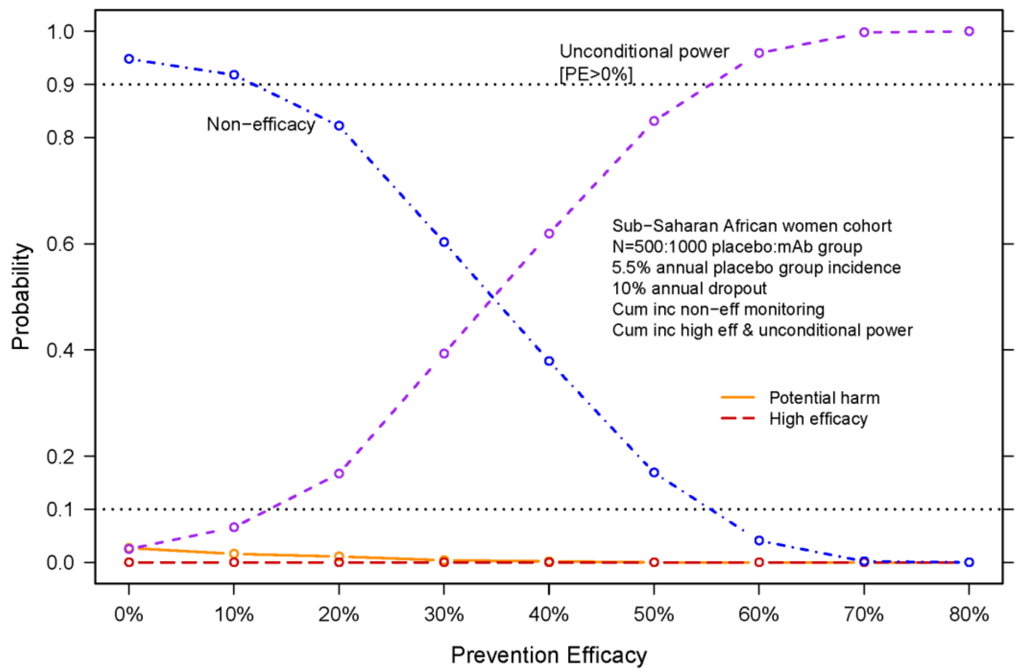


Figure 4-6 [Sub-Saharan African women cohort] Probabilities of reaching each possible trial monitoring outcome, and unconditional power to reject the null hypothesis H0: PE ≤ 0% in favor of the alternative hypothesis H1: PE > 0%, pooling over the two mAb groups

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

		Weed Out at Interim Analysis			
		Potential Harm	Non-Efficacy	High Efficacy	Unconditional Power
PE	HR	PE < 0%	PE < 40%	PE > 70%	PE > 0%
	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

		Weed Out at Interim Analysis			
		Potential Harm	Non-Efficacy	High Efficacy	Unconditional Power
PE	HR	PE < 0%	PE < 40%	PE > 70%	PE > 0%
	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 H0: PE10 ≤ 0% versus the alternative hypothesis H1: PE10 > 0% (or, equivalently, the null hypothesis H0: PE30 ≤ 0% versus the alternative hypothesis H1: PE30 > 0%), where PE10 and PE30 measure prevention efficacy in each mAb group separately.

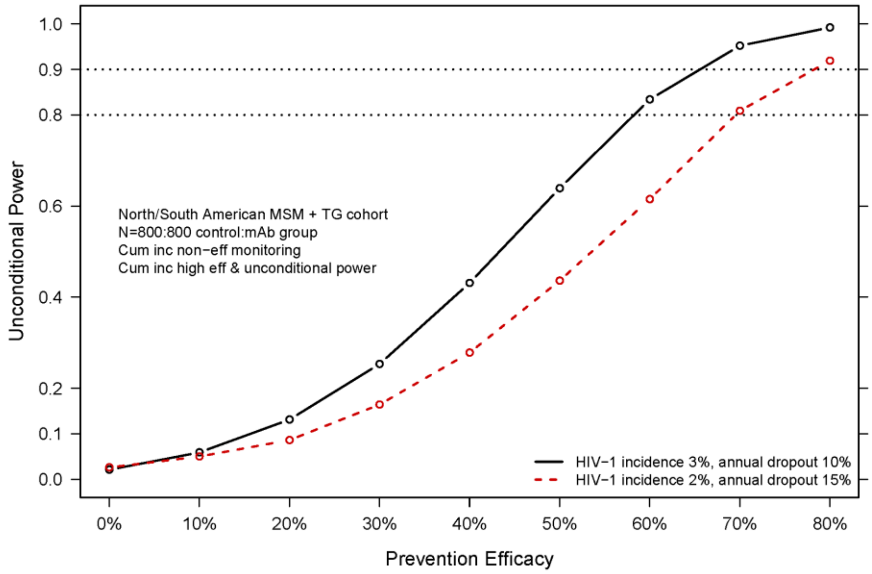


Figure 4-7 For the North/South American MSM + TG cohort and each mAb group separately, power for rejecting H0: PE10 ≤ 0% in favor of H1: PE10 > 0% (or H0: PE30 ≤ 0% in favor of H1: PE30 > 0%) based on primary assumptions about HIV-1 incidence rate and dropout rate. A power curve is also shown for a scenario with a lower than expected HIV-1 incidence rate and a higher than expected dropout rate.

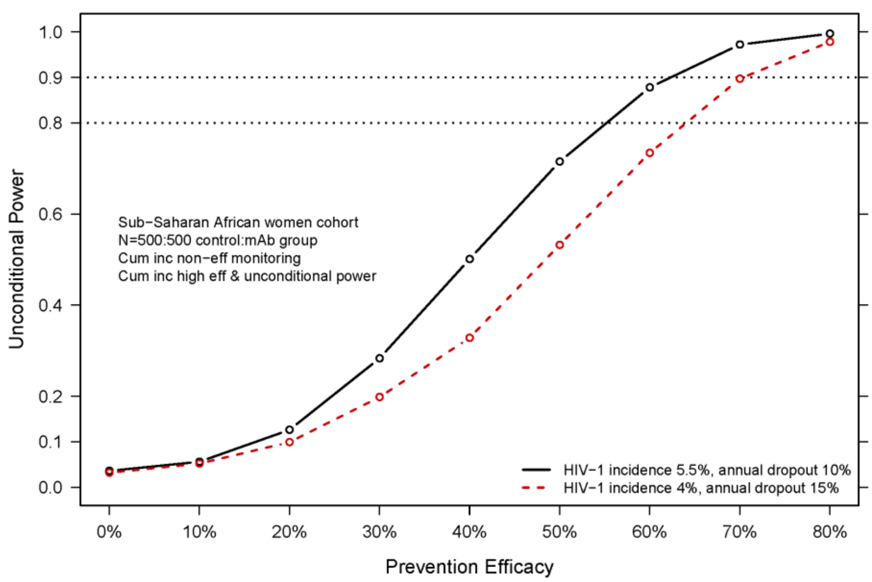


Figure 4-8 For the sub-Saharan African women cohort and each mAb group separately, power for rejecting H0: PE10 ≤ 0% in favor of H1: PE10 > 0% (or H0: PE30 ≤ 0% in favor of H1: PE30 > 0%) based on primary assumptions about HIV-1 incidence rate and dropout rate. A power curve is also shown for a scenario 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.

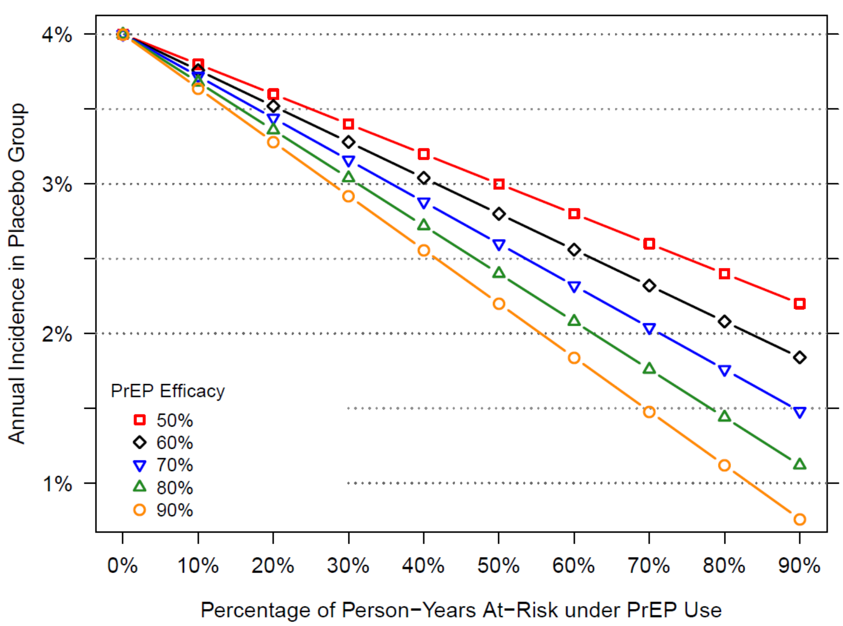


Figure 4-9 Annual HIV-1 incidence in the North/South American MSM + TG control group assuming 4% annual HIV-1 incidence in the hypothetical scenario of no PrEP use, under different levels of PrEP use and levels of PrEP efficacy

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 n1 = 800 (or the combined mAb groups n2 = 1600) and a control group of size n0 = 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 (n0 = 800)	Observed event rate in single mAb group (n1 = 800)	Observed event rate in combined mAb groups (n2 = 1600)	Rate difference (mAb group – control)	95 % CI (n1 = 800)	95% CI (n2 = 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.

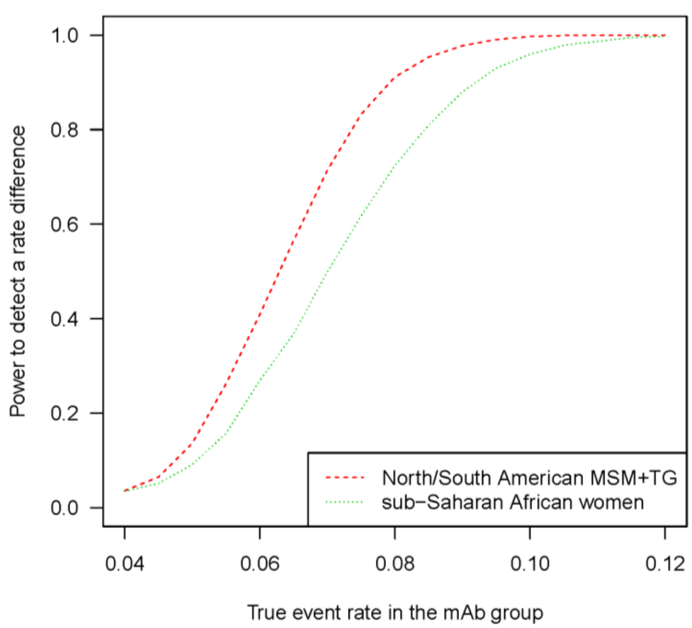


Figure 4-10 Power to detect a greater SAE rate in a mAb group versus the control group for each cohort given a 4% SAE rate in the control group

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) ≤ 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 ≥ 0% vs H1: PE < 0%	Exact 1-sided binomial test of the fraction of infections assigned to receive the mAb	1-sided α = 0.05	Constant p-value cut-off controlling the FWER at α = 0.05	After every infection from 10th until first non-efficacy analysis
Non-Efficacy	H0: PE ≥ 40% vs H1: PE < 40%	Wald test	1-sided α = 0.025	Nominal 95% CI supplemented with conditional power	4-monthly tarting when H0 may be rejected with Est. PE = 0%
High Efficacy	H0: PE ≤ 70% vs H1: PE > 70%	Wald test	1-sided α = 0.025	Nominal 95% CI	4-monthly starting at the same time as for non-efficacy

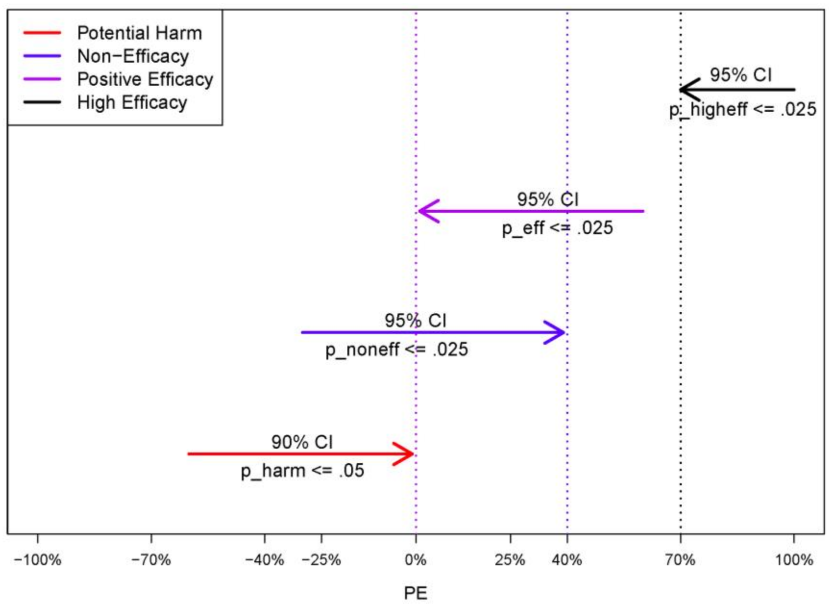


Figure 4-11 Stopping boundaries for the sequential monitoring of each study cohort

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 H0: PE ≤ 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 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 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 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

$$H0: PE(S(t) = s) = PE \text{ versus } H1: PE(S(t) = s) \text{ varies in } s. \quad (1)$$

Rejecting H0 in favor of H1 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 μg/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 PE10 = PE30 = 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 PE10 = PE30 = (30%, 60%, 80%) in these zones. The power curves also account for noise in the measurement of S(t) via a parameter rho 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.

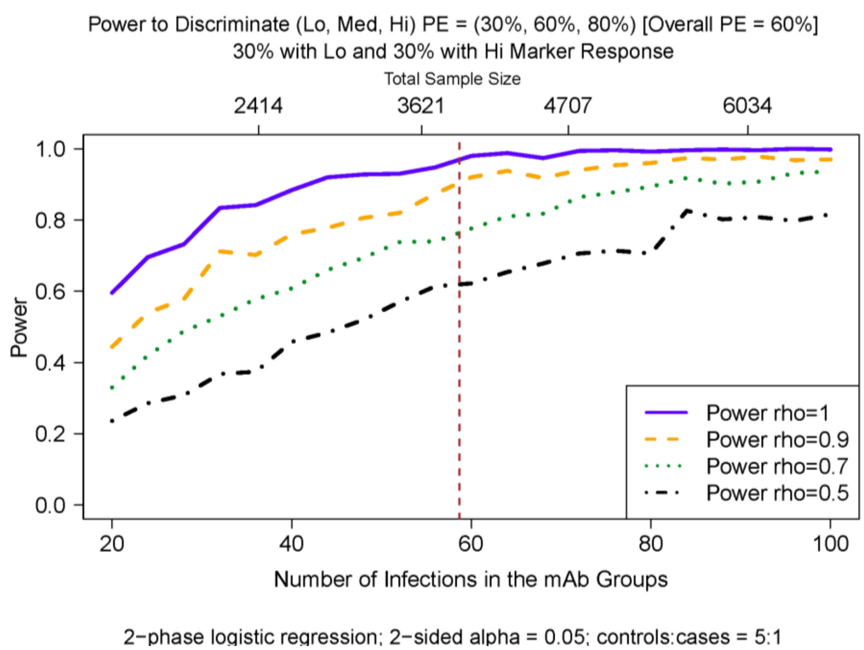


Figure 4-13 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups S(t)=Low, S(t) = Medium, and S(t) = High, for a marker with assay noise parameter rho = 1 (perfect marker), 0.9, 0.7, and 0.5 and percentages of person-years at risk in the (Low, Medium, High) marker 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.

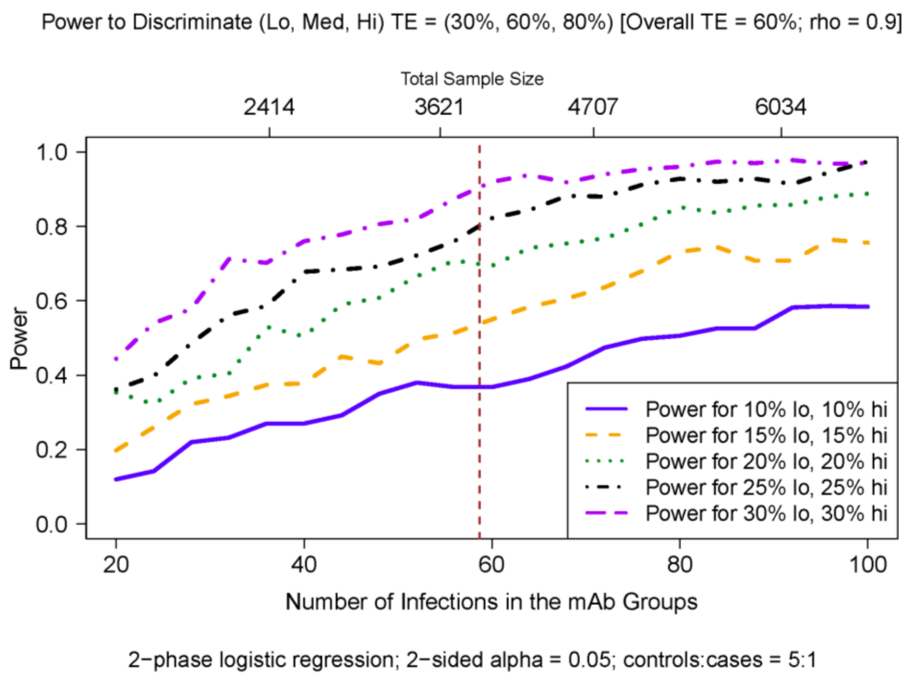


Figure 4-14 Power of the trial for detecting that PE varies over the three mAb marker-defined subgroups S(t) = Low, S(t) = Medium, and S(t) = High, for a marker with assay noise parameter rho = 0.9 and percentages of person-years at risk in the Low and High marker regions varied from 10%, 15%, 20%, 25%, 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.

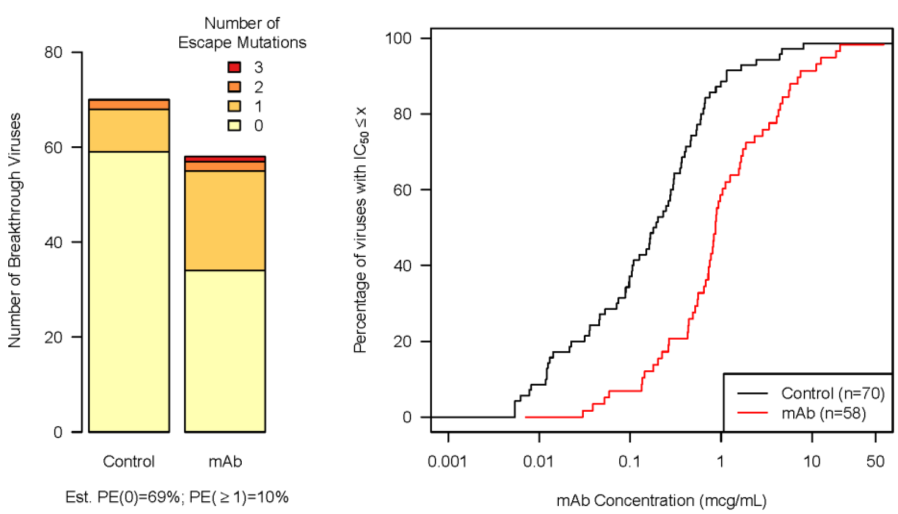
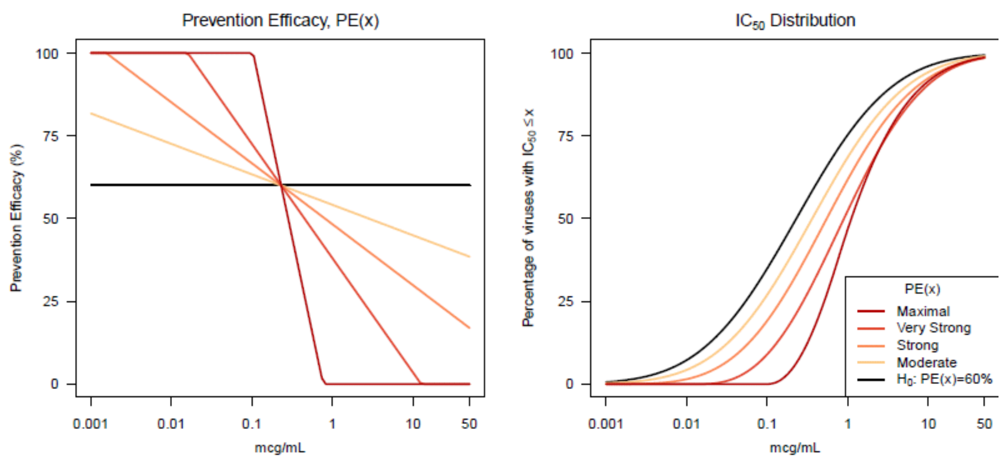


Figure 4-15 Illustration of genotypic (left panel) and phenotypic (right panel) sieve analysis, where the left panel shows the distribution of the number of known neutralization escape mutations in breakthrough control and mAb group HIV-1 sequences, and the right panel shows the percentage of the panel of breakthrough HIV-1s that are neutralized at level 50% (IC_{50}) 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)				
	Number of control cases			
PE(x)	**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** ≥ 100,000 cells/mm^3

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 mg/kg x 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 mg/kg x 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 cm^2 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-idiotype 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, rilpivarine), 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

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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

			Weeks after first IV								
Group	**Dose**	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 ⅔ 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)

6 months 1 year 1½ years

Procedure	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	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	√	√		√			√		√		√		√		√		√		√		√		√			√

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:	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	
				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	D588	D616	D644	
				Week:		W0	W4	W8		W12	W16	W20	W24	W28	W32	W36	W40	W44	W48	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	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	20	**260**
Safety labs																															
CBC/ Differential	Local lab	Local lab	EDTA	5mL	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	—	—	—	—	—	**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	—	**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	**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	**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	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	—	—	—	
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 repository

[2] 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

Procedure	Ship to[1,2]	Assay location[2]	Tube Type[3]	Tube size (vol. capacity)[3]	Visit: #.X[5] / Days after diagnosis: D0 / Weeks after diagnosis: W0	201 / D7 / W1	202 / D14 / W2	203 / D21 / W3	204 / D35 / W5	205 / D49 / W7	206 / D77 / W11	207 / D105 / W15	208 / D161 / W23	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	**80**
CD4+T cell count	Local Lab	Local Lab	EDTA	5mL	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	**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	**153**
Viral isolation/sequencing	CSR	TBD	EDTA	10mL	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	**161.5**
Plasma	CSR		EDTA	5mL	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	
				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]**				**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	**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 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	—	—	—	—	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.