HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 116

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

DAIDS DOCUMENT ID 20733

IND 125,494 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

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

STUDY PRODUCTS PROVIDED BY

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

August 3, 2018
FINAL
HVTN 116, Version 2.0

Contents

1 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of HIV prevention clinical trials. The HIV Vaccine Trials Network (HVTN) has addressed ethical concerns in the following ways:

- HVTN trials are designed and conducted to enhance the knowledge base necessary to find new methods for preventing HIV, using methods that are scientifically rigorous and valid, and in accordance with Good Clinical Practice (GCP) guidelines.

- HVTN scientists and operational staff incorporate the philosophies underlying major codes (1-3), declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV prevention clinical trials.

- HVTN 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. Community Advisory Boards (CAB) are required by DAIDS and supported at all HVTN research sites to ensure community input, in accordance with Good Participatory Practices (GPP) and all local and national guidelines."

- HVTN 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 HVTN requires that all international HVTN sites lacking national plans for providing antiretroviral therapy (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 HVTN. If a program for ART provision 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 HVTN provides 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, HVTN trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.

- HVTN trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.

- The HVTN designs its research to minimize risk and maximize benefit to both study participants and their local communities. For example, HVTN 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. HVTN protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.

- HVTN 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 HVTN trials are able to conduct other critical research in their local research settings.

- The HVTN values the role of in-country Institutional Review Boards (IRBs), Ethics Committees (ECs), and other Regulatory Entities (REs) as custodians responsible for ensuring the ethical conduct of research in each setting.

2 IRB/EC review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs/REs 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 HVTN Investigator welcomes IRB/EC/RE questions or concerns regarding these research requirements.

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

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

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

2.1 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 postinfusion and collecting information regarding side effects for several days postinfusion; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, 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.

2.2 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.

2.3 Equitable participant 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.

2.4 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 9.1). Each site is provided training in informed consent by the HVTN as part of its entering the HVTN. The HVTN requires a signed consent document for documentation, in addition to chart notes or a consent checklist.

2.5 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 11.1). Safety is monitored daily by HVTN Core and routinely by the HVTN 116 Protocol Safety Review Team (PSRT). In addition, the HVTN Safety Monitoring Board (SMB) periodically reviews study data.

2.6 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 and Appendix B). 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, a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena, protects research participants in HVTN protocols. 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 and Specimens with the HVTN 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.

3 Overview

Title

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

Primary objectives and endpoints

Primary objective 1

- To evaluate the safety and tolerability of VRC01/VRC01LS mAb administered through IV infusion

Primary endpoint 1

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

Primary objective 2

- For each sex at birth, to evaluate the pharmacokinetics of VRC01 in serum versus mucosa in each mucosal compartment

Primary endpoints 2 (Groups 1 & 2 & 4)

- Serum concentration of VRC01 out to Month 6 after the last infusion

- Levels of VRC01 in genital and rectal secretions, as well as cervical, vaginal, and rectal tissues at the collection timepoints

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 intravenously (IV)

- **VRC01LS:** human monoclonal antibody (mAb) VRC-HIVMAB080-00-AB in formulation buffer at pH 5.8 in sufficient normal saline (Sodium Chloride for Injection 0.9%, USP) to be administered IV

Table 3-1 Schema

Group	Treatment	Infusion schedule (Months)					
		N	M0	M2	M3	M4	M6
Group 1	VRC01 10 mg/kg	23	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 2	VRC01 30 mg/kg	23	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 3	VRC01LS 30 mg/kg	~6*	IV Infusion		IV Infusion		IV Infusion
Group 4	VRC01 30 mg/kg	16	IV Infusion				
Group 5	VRC01LS 30 mg/kg	~6*	IV Infusion				

*Enrollment will stop in Groups 3 and 5 when ≥12 volunteers have been enrolled across *both* groups (see Section 6.1).

Participants

About 74 healthy, HIV-uninfected adult volunteers aged 18 to 50 years, regardless of sex or gender

Design

Multicenter, randomized, open-label trial

Duration per participant

As VRC01LS is designed to have a longer half-life than VRC01, participants who receive VRC01 will be followed for 6 months after the last product administration and participants who receive VRC01LS will be followed for 12 months after the last product administration. Specifically,

Groups 1, 2, and 5: 12 months of scheduled clinic visits

Group 3: 18 months of scheduled clinic visits

Group 4: 6 months of scheduled clinic visits

Estimated total study duration

40 months (includes enrollment and follow-up)

Investigational New Drug (IND) sponsor

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

Study products provider

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

Core operations

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

HVTN Laboratory Center (LC)

- **HIV diagnostic laboratories**
  - University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)
  - HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (HSML-NICD) (Johannesburg, South Africa)
- **Endpoint assay laboratories**
  - Duke University Medical Center (Durham, North Carolina, USA)
  - FHCRC/University of Washington (Seattle, Washington, USA)
  - Cape Town HVTN Immunology Laboratory (CHIL) (Cape Town, South Africa)
  - NIAID Vaccine Immune T-Cell Antibody Laboratory (NVITAL) (Gaithersburg, Maryland, USA)
  - Vaccine Research Center (VRC) (Bethesda, Maryland, USA)

Study sites

HVTN Clinical Research Sites (HVTN CRSs) in the US and South Africa to be specified in the Site Announcement Memo

Safety monitoring

HVTN 116 PSRT; HVTN Safety Monitoring Board (SMB)

3.1 Protocol Team

Protocol leadership

Chair	Julie McElrath Seattle Vaccine Trials Unit 206-667-6704 jmcelrat@fredhutch.org	*Biostatistician*	Yunda Huang SCHARP, FHCRC 206-667-5780 yunda@scharp.org
Cochair	Linda-Gail Bekker Desmond Tutu HIV Centre +27 21 6506966 Linda-Gail.Bekker@hiv-research.org.za	*Medical officer*	Julia Hutter DAIDS, NIAID 240-627-3039 julia.hutter@nih.gov
Protocol Team leader and Core medical monitor	Philipp Mann HVTN Core, FHCRC 206-667-1651 pmann@fredhutch.org	*Laboratory lead*	John Hural HVTN Laboratory Program 206-667-1683 jhural@fredhutch.org

Other contributors to the original protocol

Vaccine developer representatives	Julie Ledgerwood VRC	*Clinical safety specialist*	Megan Jones HVTN Core, FHCRC
	Barney Graham VRC	*Clinical trials managers*	Carissa Karg HVTN Core, FHCRC
Laboratory Program representatives	On Ho HVTN Laboratory Program, FHCRC		Charlie Gregor HVTN Core, FHCRC
	Rena Astronomo HVTN Laboratory Program, FHCRC	*SDMC Project manager*	Evangelyn Nkwopara SCHARP, FHCRC
	Maria Lemos HVTN Laboratory Program, FHCRC	*Clinic coordinators*	Julie Czartoski Seattle CRS
	Mary Gross HVTN Laboratory Program, FHCRC		Maureen Rattley Cape Town Groote Schuur CRS
Regulatory affairs	Meg Brandon HVTN Core, FHCRC	*HVTN SDMC program manager*	Gina Escamilla SCHARP, FHCRC
Community Advisory Board (CAB) members	Richard Laboy Philadelphia CAB	*Protocol development manager*	Ryan Jensen HVTN Core, FHCRC
	Dana Atkins Seattle CAB	*Community engagement unit representative*	Gail Broder HVTN Core, FHCRC
DAIDS protocol pharmacist	Lynette Purdue DAIDS, NIAID 240-627-3061	*Community educator/recruiter*	Brian Kanyemba Cape Town Groote Schuur CRS
Statistical research associate	Abby Isaacs SCHARP, FHCRC	*Technical editor*	Erik Schwab HVTN Core, FHCRC

4 Background

4.1 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 with access to the full toolkit of proven prevention approaches (4-6).

Most HIV transmissions occur sexually and therefore involve the transmission of HIV across the epithelium of the vagina/cervix, rectum/distal colon, or penis. The colon and cervix are lined by a columnar epithelium, which protects a large pool of HIV target cells, such as activated CD4+ T cells, dendritic cells and macrophages. In contrast, the vagina and penis have stratified epithelium, protecting a less dense concentration of HIV target cells. Thus, whereas receptive anal sex has the highest probability of HIV-1 transmission (0.4-3.38%), receptive vaginal sex is associated with intermediate transmission probability (0.018-0.150%), and transmission probability is lowest for insertive penile exposure (0.003-0.009%) (7-9).

The central role of mucosal sites in HIV-1 transmission and early infection underscores the need for prevention approaches that protect mucosal sites from infection. Humoral and cellular responses in mucosal compartments have been analyzed by the HVTN in earlier HIV vaccine trials. Participants of HVTN 069 (a phase 1 HIV vaccine trial evaluating DNA and Ad5 containing regimens) at the Seattle site were offered enrollment into a companion mucosal study, and HVTN 076 was specifically designed to evaluate mucosal responses to the vaccine regimen of a large scale efficacy study, HVTN 505, that was ongoing in parallel. As it is challenging to perform in-depth mucosal evaluations within the framework and study participant risk profile of a large scale efficacy trial, a scientifically and operationally sound approach is the strategy taken with HVTN 076 and proposed here: a smaller scale study looking at the congruent intervention in a stringently designed phase 1 study that allows the consistent evaluation of mucosal samples.

An alternative approach from active vaccination to the prevention and/or treatment of infectious diseases is passive administration of antibodies, a strategy that has been employed for more than 100 years against diverse disease targets and that is still used for hepatitis A and B prophylaxis (10, 11) and for postexposure prophylaxis (PEP) for rabies, measles, varicella zoster, and other infectious diseases (12). Most notably, palivizumab has been used for respiratory syncytial virus (RSV) infection 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 infection season can reduce RSV-associated hospitalizations by 39–78% in premature infants and in children with bronchopulmonary dysplasia (13). Subsequent studies have

confirmed palivizumab's safety, efficacy, and clinical benefit for infants at high risk for RSV infection (14, 15). Hence, palivizumab serves as a contemporary model for the use of mAbs to block a mucosally-acquired infection.

Over the past several years, there has been a concerted and successful effort to isolate broadly neutralizing antibodies (bNAbs) to HIV-1 from chronically infected donors (16-28). Notably, many of these bNAbs are substantially more potent and have broader coverage of circulating HIV-1 strains than the first generation of bNAbs discovered in the 1990s. Subsequent research has provided considerable insight into the sites these antibodies target on the HIV-1 envelope glycoprotein and their functionality (ie, the mechanisms by which they neutralize the virus) (19, 20, 29, 30). This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies (31-34), prompting optimism that vaccines that elicit bNAbs against HIV-1 can be developed (32, 35). In addition, the availability of safe and potent 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 monoclonal antibody (mAb), which is targeted against the HIV-1 envelope (Env) CD4-binding site (18). This mAb was originally discovered in a person with chronic HIV-1 infection who maintained HIV-1 control without use of ARV therapy (36). By applying a novel method of isolating B cells that produce a specific antibody and recombinant DNA technology, the heavy and light chains encoding VRC01 were cloned and sequenced, allowing the synthetic production of codon-optimized genes encoding the Env variable regions that were inserted into proprietary immunoglobulin G1 (IgG1) backbone sequences (18). Since the isolation of the VRC01 antibody, subsequent work evaluating longitudinal serum collected from HIV-1–infected individuals has demonstrated that although antibodies capable of binding to VRC01-like epitopes may be induced during HIV-1 infection, they occur in only a minority of HIV-infected individuals and may take years to develop (37). VRC01 will be evaluated for safety and HIV-1 prevention in the HVTN 703/HPTN 081 and HVTN 704/HPTN 085 efficacy trials (see section 4.4).

Recently, the VRC has developed a VRC01 variant, designated VRC01LS, which was designed to have a longer half-life by exploiting the functions of the neonatal Fc receptor (FcRn). The FcRn regulates the half-life of IgG antibodies through pH-dependent binding to IgG Fc regions, which favors binding at low pH (eg, lysosomal compartments and vaginal lumen) and release at neutral pH (eg, peripheral blood) (38). The FcRn is expressed in endothelial cells of the vasculature and some myeloid cells, where it can rescue IgG from lysosomal degradation by binding these molecules within this low pH compartment, then releasing them back into circulation (39-41). In the intestinal epithelium, the FcRn transports IgG bi-directionally: it transports IgG into the intestinal lumen and it recycles complexed antibody back to the tissue to support the induction of immunity, tolerance and/or susceptibility (42-44). In the genital tract, FcRn is expressed on columnar epithelial cells lining the human penile urethra (45) and

the endocervix, as well as on reserve epithelial cells lining the vagina. Thus, the tissue distribution of FcRn enables the delivery of IgG to relevant mucosal compartments and may thereby contribute to protection or susceptibility; the latter possibility has been suggested in the case of non-neutralizing Abs which may mediate the transmission of bound, infectious particles via FcRn transport pathways (46-48).

The LS mutation (M428L / N434S) to the constant region of the VRC01 antibody enhances its binding affinity for FcRn at low pH, yet does not affect its release at pH 7.4 (49). Thus, the LS modification was found to alter antibody turnover in nonhuman primate (NHP) models, with increased persistence in serum and slower decay in rectal and cervicovaginal tissue. Intravenous administration of VRC01LS also afforded increased protection against intra-rectal challenge with simian-human immunodeficiency virus (SHIV). Consequently, the increased persistence of anti-HIV neutralizing antibodies in mucosal tissue could have significant operational benefits, as increased maintenance at the portals of entry will allow for consistent protective levels with less frequent administrations and/or reduced dosing.

4.2 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. VRC01 is an IgG1 antibody and is highly somatically mutated from the germ-line precursor.

The VRC01 antibody has been well characterized preclinically and exhibits favorable potency and half-life characteristics, which are important for the feasibility of a passive immunization approach (19). Figure 4-1 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 4-2 and Table 4-1, 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. In addition, VRC01 has demonstrated significant protection against both intravaginal and intrarectal SHIV challenge in NHP models (see Section 4.6.1).

While virus neutralization potency measured *in vitro* is not absolutely predictive of protection *in vivo*, several NHP challenge studies with a number of bNAbs have shown that plasma neutralization titers correlate well with *in vivo* protection. In a recent study, Shingai et al. calculated that a modest plasma neutralizing IC50 titer of ~1:100 could protect 50% of NHP from a high dose IR SHIV challenge (50). This value is based upon the combined results from 60 macaques recipients of 5 different bNAbs, including VRC01, and challenged with either of two R5-tropic SHIVs. The value may thus serve as a rough guide for predicting protection based on plasma neutralizing Ab titers. However, it should be noted that other studies have reported both higher (eg ~1:200-1:495 neutralization IC_{50} titer for PGT121) and lower plasma requirements (eg ~ 35 times neutralization IC_{50} for VRC01) to achieve protection against mucosal challenge (51, 52). Discrepancies may, in part, reflect imperfect correlations between Ab levels found in circulation and in mucosal tissues. Furthermore, the challenge doses used in these studies are orders of magnitude higher than what is considered physiologically relevant for HIV-1 mucosal transmission. Nonetheless, according to the 1:100 plasma neutralization titer estimate, modest plasma concentrations of VRC01 (~30-50 mcg/mL) may provide protection against the majority of virus isolates tested.

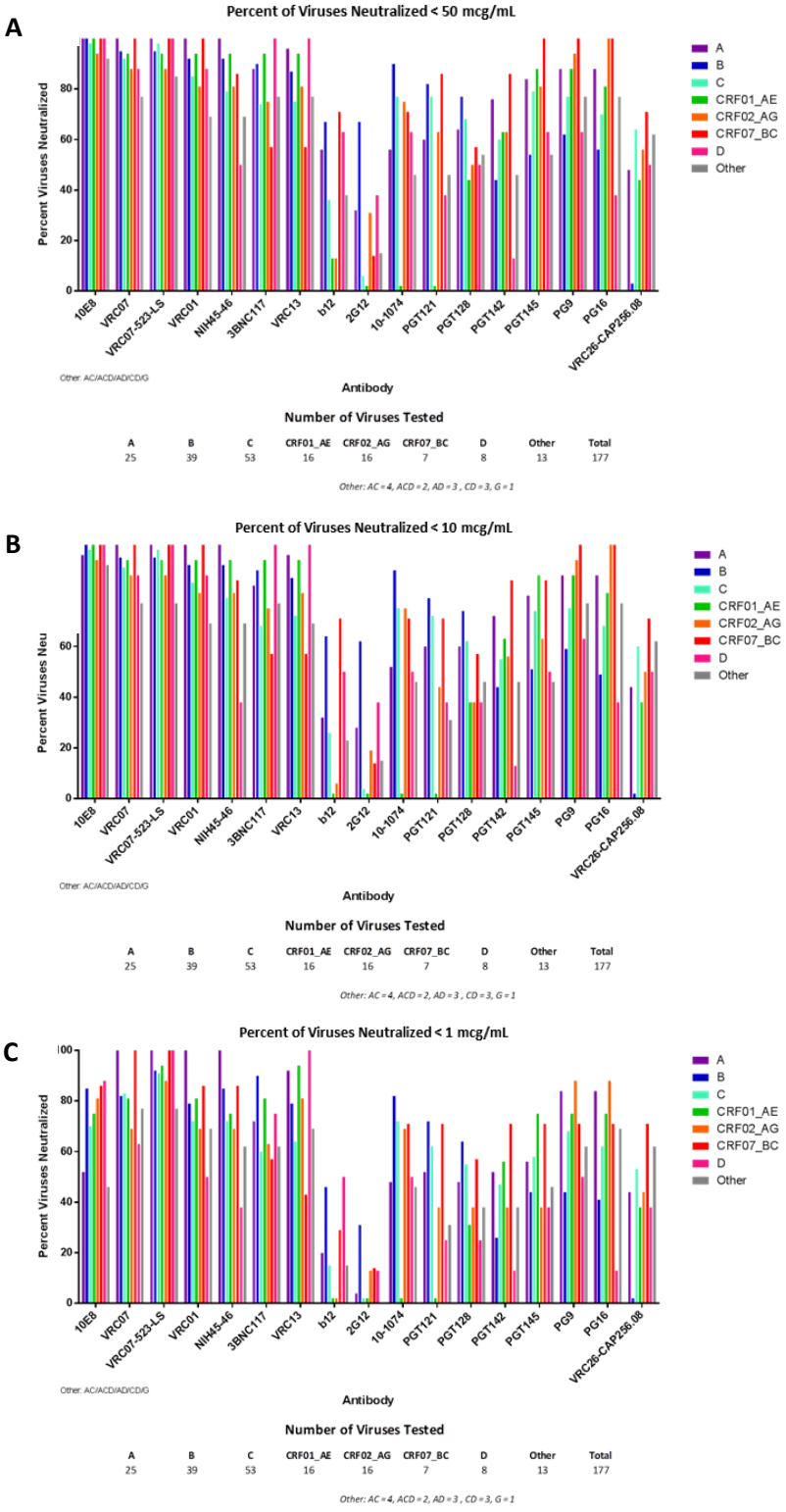

Figure 4-1 Percentage of viruses neutralized at different serum concentrations. (A) < 50 mcg/mL; (B) < 10 mcg/mL; (C) < 1 mcg/mL.

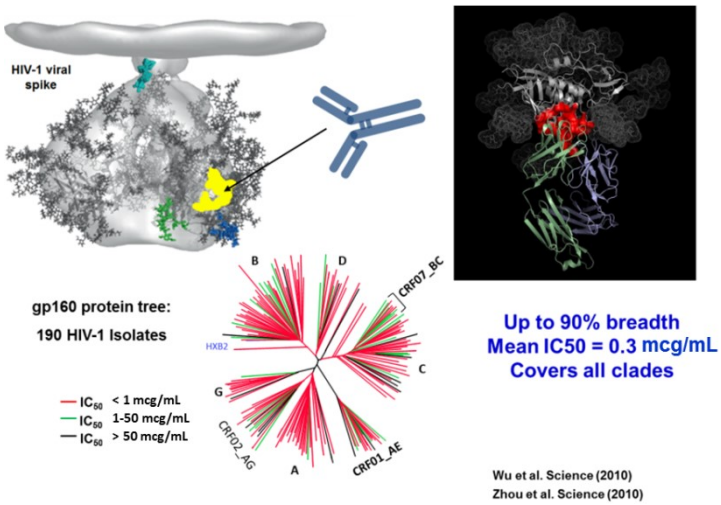

Figure 4-2 CD4 binding site antibody: VRC01 with binding site on Env, in situ structure, and cross clade IC_{50} (18, 19)

Table 4-1 Distribution of IC_{50} values across clades

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%**

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

4.3 VRC01LS: VRC-HIVMAB080-00-AB

VRC01LS is a broadly neutralizing human MAb targeted against the HIV-1 CD4 binding site. It was developed by VRC/NIAID/NIH.

VRC01 was modified by site-directed mutagenesis to increase its binding affinity for the neonatal Fc receptor (FcRn); the resulting antibody is designated VRC01LS. The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region far outside of the antigen-combining site (53). The VRC01LS is an IgG1, and the glycosylation pattern is derived from its production in a Chinese Hamster Ovary (CHO) mammalian cell line.

While the LS mutation confers enhanced FcRn binding capability to the bNAb and allows its efficient transport to and accumulation in mucosal compartments, VRC01LS displays normal binding to other FcRs, such as FcγRIIIa, thus not impeding ADCC activity. The VRC01LS variant also retains comparable neutralization breadth and potency to wild-type (WT) VRC01. In Indian rhesus macaques, the LS mutant exhibited a 2.5-fold longer half-life (VRC01, 4.65 days; VRC01-LS, 11.80 days) and a 2.5-fold slower clearance rate than the wild type mAb (VRC01, 16.52 ml day-1 kg-1; VRC01-LS, 6.47 ml day-1 kg-1). The LS variant also persisted in rectal mucosal tissues for more than 70 days whereas the VRC01 (WT) antibody was undetectable at day 28 (49).

The bulk lot of the drug substance was manufactured under cGMP using a stably transfected CHO cell line, purified, and the drug product vials were filled and labeled at the VRC, Vaccine Clinical Material Program operated by Leidos Biomedical Research, Inc., Frederick, MD. Each product vial contains 6.25 mL volume at a concentration of 100 mg/mL VRC01LS in formulation buffer containing 25 mM Sodium Citrate, 50 mM Sodium Chloride, and 150 mM L-Arginine Hydrochloride at pH 5.8.

Details on VRC01LS composition and manufacturing can be found in the IB.

4.4 Trial design rationale

Two large scale phase 2b efficacy studies of VRC01 opened in parallel in 2016. HVTN 703/HPTN 081 enrolled the first participant on May 17, 2016, and will enroll 1900 participants at risk of contracting HIV-1 infection in Sub Saharan Africa; whereas HVTN 704/HPTN 085 will enroll 2700 participants at risk of contracting HIV-1 infection in the Americas and Switzerland. HVTN 704/HPTN 085 opened for accrual on March 31st 2016, and the first participant was enrolled on April 6th 2016. Both studies will evaluate the ability of two different IV doses (10 mg/kg and 30 mg/kg, administered every 8 weeks) of VRC01 to prevent HIV-1 infection. Since the target populations for HVTN 703/HPTN 081 and HVTN 704/HPTN 085 predominantly acquire HIV-1 infection through sexual exposure, the concentration and function of Abs in the rectal and genital mucosae following systemic administration are potentially key to the effectiveness of the passive immunoprophylaxis approach. While phase 1-2a studies have collected limited samples to measure Ab levels in human mucosal secretions, there is very little data (recently generated in a Mucosal Sub-study to HVTN 104) on the Ab levels or distribution in human mucosal tissues, which serve as critical portal of entry for HIV-1 infection. Mucosal biopsies cannot be performed in the context of an efficacy trial enrolling high risk individuals because of potential alterations in risk of infection; however, HVTN 116 presents a crucial opportunity to examine the pharmacokinetic behavior and functionality of VRC01 and VRC01LS in mucosal tissues.

In parallel with HVTN 703/HPTN 081 and HVTN 704/HPTN 085, it is desirable to gather in-depth data on the distribution and persistence, as well as the

functionality of VRC01 in mucosal secretions and tissues at the dosages planned in the phase 2b trial. HVTN 116 will investigate concentrations and tissue distributions of the VRC01 antibody in mucosal tissues that are common sites of HIV exposure, and compare these to paired serum levels. HVTN 703/HPTN 081 and HVTN 704/HPTN 085 will establish serum antibody levels and correlate those with protection. However, a correlation between HIV prevention, the serum antibody levels, and the mucosal antibody levels of the VRC01 antibody cannot be established in these efficacy trials alone. HVTN 116, which includes arms that mirror the infusion schedule of HVTN 703/HPTN081 and HVTN 704/HPTN 085, can bridge the gap from serum to mucosal levels and therefore help us in understanding the underlying biological tenets of Antibody Mediated Protection (AMP), particularly with respect to mucosal challenge. Furthermore, HVTN 116 will give us the opportunity to investigate a novel variant, designated VRC01LS, with enhanced FcRn binding capability. HVTN 116 will therefore compare serum and mucosal pharmacokinetics and functionality of this LS variant of the antibody to the wild-type VRC01 antibody, in single- and repeated-dose regimens of 30mg/kg.

Generally, the minimum number of biopsies needed in order to conduct measurements of levels is 1 per tissue, for immunohistochemistry it is also 1 per tissue, and for the infectivity assays the numbers we propose are 3 for colon, 3 for vagina, and 2 for cervix. Due to the uneven distribution of vasculature, FcRs and immune aggregates in tissue, we expect mucosal biopsies to display increased variability in infectivity challenge assays. Therefore, replicates are essential. The necessity of replicates was illustrated by the rectal explant infections we conducted on 7 male participants after VRC01 infusions in HVTN104. Upon challenge with a VRC01 sensitive virus, 4 participants demonstrated resistance to infection in 3/3 biopsies, 2 participants showed resistance in 2/3 biopsies, and 1 showed resistance in 1/3 biopsies. Consequently, the infectivity assay will need a minimum of 2 biopsies in order to evidence any partial protection.

Congruently, two ectocervical and three vaginal biopsies are requested to lend power to our ability to measure true Ab-mediated inhibition of HIV-1 infection ex vivo. In pilot experiments utilizing vaginal biopsies from participants who had not received an Ab infusion, we found that 16 of 20 vaginal biopsies collected from 5 participants were infected (one participant was sampled twice; 1 participant had 0/3 biopsies infected by the challenge virus and 1 participant had 4/5 biopsies infected). Due to the immunological heterogeneity of the mucosal tissue and the small size of the biopsies, triplicate biopsies (vaginal) are needed, whenever possible, particularly when a small number of participants is recruited for each group. Multiple collection timepoints are required to answer the following questions: what concentration of VRC01 or VRC01LS reaches mucosal sites and how quickly do these levels decay? Do functional levels reach the mucosal tissues and if so, how long are they maintained?

In summary, HVTN 116 will provide additional supportive data for planned and postulated uses of VRC01 for the prevention of HIV acquisition. The primary goals are to further validate the safety of two doses and to interrogate the

distribution, persistence, and functionality of the antibody in relevant mucosal compartments. Additionally, HVTN 116 will provide safety data for the novel variant, VRC01LS, and will establish the distribution, persistence, and functionality of this Ab in mucosal tissues.

Collections will include cervicovaginal secretions as well as cervical and vaginal biopsies (as well as rectal secretions and biopsies at the Seattle site) in those born female and the collection of rectal secretions and semen as well as rectal biopsies in those born male. The proposed timepoints will provide the opportunity to establish the mucosal levels of the respective antibodies over time, as well as the functional capabilities at peak levels and low levels.

4.4.1 Dose and schedule

The proposed VRC01 doses for this mucosal study are based on doses that are being administered in the phase 2b efficacy trials, HVTN 703/HPTN 081 and HVTN 704/HPTN 085. As these doses (10 mg/kg and 30 mg/kg) are being evaluated on a large scale, interrogating the levels and functions of the antibody when administered at these same doses in serum, mucosal secretions, and mucosal tissues will be most informative and valuable for the field.

VRC01LS should have a longer half-life, therefore the dosing interval proposed is three months compared to a two-month interval with the VRC01 wild-type antibody. This interval is considered most likely to be utilized in a prevention effort and is also applied in the VRC 606 phase 1 study (Section 4.7.2). The 30 mg/kg VRC01LS dose also allows a direct comparison with the 30 mg/kg group of VRC01.

Groups 4 and 5, with a single infusion at 30 mg/kg will provide the opportunity to compare the PK profiles of the two antibodies in a more detailed manner.

VRC01 and VRC01LS are both formulated in vials at 100mg/ml (+/- 10mg/ml). Due to the concentration of the VRC01 antibody, large volumes are required for adult dosing and therefore IV administration will be used in this study.

4.5 Preclinical safety studies

4.5.1 Preclinical toxicology and PK study of VRC01

Table 4-2 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 4-2). 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 were 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 comprised 10 male and 10 female rats. Five animals of each sex were sacrificed on Day 9, one day after the second VRC01 administration; the remaining animals were sacrificed on Day 30, 22 days after the second VRC01 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 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 about 0.28 L/kg, indicating that the drug was distributed primarily in the serum and eliminated slowly. 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 (54, 55).

4.5.2 Tissue cross reactivity of VRC01 and VRC01LS with human tissues *in vitro*

The *in vitro* preclinical safety studies performed to assess potential off target binding by VRC01 and VRC01LS are summarized in Table 4-3 and Table 4-4. VRC01LS and VRC01 were assessed in GLP tissue cross reactivity (TCR) studies using research-grade materials and tissues from a single adult human donor. VRC01LS and VRC01 showed nearly identical minimal tissue binding. There was no unexpected off -target binding.

Table 4-3 *In vitro* preclinical safety studies with VRC01

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
Normal adult and neonate human tissue cross-reactivity study	No evidence of tissue cross reactivity in the panel of normal adults and neonatal tissues tested

Table 4-4 *In vitro* preclinical safety studies with VRC01LS

Study Purpose	Study Outcome
Assessment of anti-phospholipid reactivity	VRC01LS does not react to phospholipids
Assessment of anti-nuclear antigen reactivity	VRC01LS does not react with nuclear antigens
Assessment of binding to a human epithelial cell line (HEp-2) by Immunohistochemistry	VRC01LS does not bind to HEp-2 cells
Assessment of potential "off target" binding to protein arrays microchips precoated with 9400 full-length human proteins	No clinically significant binding identified
Assessment of potential "off target" binding in a human Tissue Cross-Reactivity study with VRC01LS and VRC01	VRC01LS and VRC01 variably stained cytoplasm and cytoplasmic granules in epithelial and/or decidual cells in several human tissues. The findings were judged of no toxicologic significance for Mab as the cytoplasmic compartment is not available to Mab in vivo.

4.6 Nonhuman primate studies

4.6.1 NHP studies of VRC01

Several non-GLP studies of VRC01 have been completed in NHP to assess for plasma and secretion concentrations and for preclinical data to support potential efficacy for prevention of HIV infection. Table 4-5 summarizes the studies performed and supports the plan to evaluate up to 40 mg/kg administered IV as a dose range of potential interest for a preventive indication. The current assay being used to detect VRC01 in serum has a lower limit of quantitation (LOQ) of 1.1mcg/mL. Detectable concentrations of VRC01 were measured in vaginal, rectal, nasal and saliva samples after IV administration of 20 mg/kg of VRC01. Concentrations of VRC01 were lower in mucosal samples after IV administration of 5 mg/kg of VRC01. Please refer to the VRC01 IB for more details.

Table 4-5 Preclinical proof-of-concept studies performed with VRC01 mAb in NHP models

Study Purpose	Study Outcome
Demonstration of plasma and secretion concentrations of VRC01 given intravenously at two dose levels in male rhesus macaques	Kinetics of decay of VRC01 administered IV at 5 mg/kg and 20 mg/kg in plasma, nasal and rectal secretions, and saliva established
Demonstration of plasma and secretion concentrations of VRC01 given by IV or SC routes in female rhesus macaques	Kinetics of decay of 40 mg/kg of VRC01 given IV or SC in plasma, rectal, vaginal and nasal secretions established
Demonstration of challenge-protection against intrarectal high-dose SHIV SF162P3 in male rhesus macaques	100% protection from challenge demonstrated at 20 mg/kg dose administered IV
Demonstration of challenge-protection against intravaginal high-dose SHIV SF162P3 in female rhesus macaques	100% protection from challenge demonstrated at 20 mg/kg dose administered IV
Demonstration of challenge-protection against intrarectal high-dose SHIV BaL in rhesus male macaques	100% protection from challenge demonstrated at 20 mg/kg dose administered IV

4.6.2 NHP studies of VRC01LS

Several non-GLP studies have been conducted in NHP models to evaluate potential efficacy of VRC01LS for prevention of HIV infection.

Table 4-6 summarizes the studies performed to date, which support plans to evaluate up to 40 mg/kg dose administered IV as a dose range of potential interest for a preventive or therapeutic indication.

One investigation in NHP assessed the concentrations of VRC01, VRC01LS, and VRC01IHH (a mutation with an FcRn binding knockout) in serum and rectal tissue in female rhesus macaques. Three groups of NHP were administered a single IV dose of 10 mg/kg of either VRC01 (n=4), VRC01LS (n=4) or VRC01-IHH (n=2). Introduction of the LS mutation increased half-life 2.5-fold (VRC01: 4.65 days, VRC01LS: 11.80 days) and reduced clearance approximately 3-fold compared to the WT (VRC01: 16.52 mL/day/kg, VRC01LS: 6.47 mL/day/kg). In contrast, VRC01IHH displayed markedly reduced persistence (see Figure 4-3a). The levels of VRC01 (WT), VRC01LS (LS) and VRC01-IHH (IHH) were measured in the rectal tissues. The amount of each mAb was normalized relative to total tissue protein. As shown Figure 4-3b, VRC01LS remained detectable in rectal tissue for more than 70 days and persisted at significantly higher levels ($p<0.001$, t-test), while the VRC01 (WT) could not be measured after 28 days. VRC01-IHH could not be detected in rectal tissues after 14 days.

Table 4-6 Pre-clinical proof-of-concept studies performed with VRC01LS in NHP models

Study Purpose	Study Outcome
Determine whether VRC01LS could protect male Rhesus Macaques against SHIV infection more effectively than VRC01 after IV administration of low sub-optimal protective dose (0.3 mg/kg) of MAb	10/12 and 5/12 NHP were infected after receiving VRC01 and VRC01LS respectively. VRC01LS conferred superior protection against SHIV infection compared to VRC01. Levels of VRC01LS in rectal tissues were higher compared to levels of VRC01.
Determine serum and rectal tissue concentrations in Indian rhesus macaques administered 10 mg/kg of VRC01 or VRC01LS IV	Introduction of the LS mutation increased the serum half-life of VRC01LS 2.5-fold and reduced clearance 3-fold compared to VRC01. VRC01LS remained detectable in rectal tissue for more than 70 days and persisted at significantly higher levels, while the VRC01 (WT) was not detectable after 28 days (49).
Determine serum and mucosal sample concentrations in female cynomolgus macaques administered 10 mg/kg of VRC01 or VRC01LS IV	When administered IV at a single dose of 10 mg/mL in cynomolgus macaques, the half-life of VRC01LS was about 30 days, a 3-fold increase compared to VRC01. Increased levels of VRC01LS were noted in rectal tissue, rectal secretions and vaginal tissue at 28 days post antibody infusion compared to VRC01 (49).
Determine serum and mucosal secretion concentrations in male and female rhesus macaques administered 10 mg/kg of VRC01LS SC	When administered SC at a single dose of 10 mg/kg to rhesus macaques, the half-life of VRC01LS was about 28 days and VRC01LS was found in rectal, vaginal and nasal secretions up to day 49 post administration (last day of testing).
Demonstrate SHIV challenge protection in rhesus macaques administered 20 mg/kg of VRC01LS IV	Complete protection from a rectal SHIV SF162P3 challenge was demonstrated in 5/6 animals after administration of VRC01LS at a dose of 20 mg/kg dose administered IV. The remaining animal had a single timepoint with viremia after challenge.

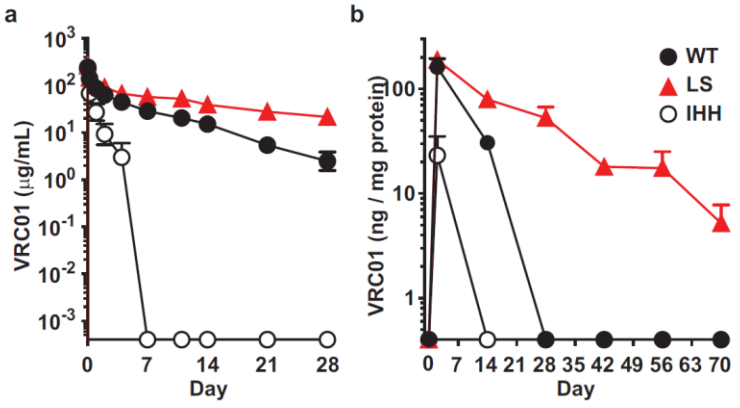

Figure 4-3 VRC01LS (LS), VRC01 (WT) and VRC01-IHH (IHH) Levels in (a) Serum and (b) Rectal Tissues in Rhesus Macaques

Another study was performed in male (n=2) and female (n=2) cynomolgus macaques. Each animal received a single 10 mg/kg dose of either VRC01 (WT) or VRC01LS, and blood samples as well as rectal secretion samples were collected through day 28 post infusion. Mucosal tissue samples (rectal or vaginal pinch biopsies) were collected at days 2, 13 and 28 post administration. The VRC01 and VRC01LS serum and mucosal concentrations are shown in Figure 4-4 and Figure 4-5. Similar to the results in rhesus macaques (described above), VRC01LS circulated 3-fold longer than VRC01 (Figure 4-4a) in serum of cynomolgus

macaques. Compared to VRC01, increased levels of VRC01LS were noted in rectal tissue (Figure 4-4b), rectal secretions (Figure 4-4c) and vaginal tissue (Figure 4-5) at 28 days post antibody infusion, though the rectal tissue sampling showed more consistency.

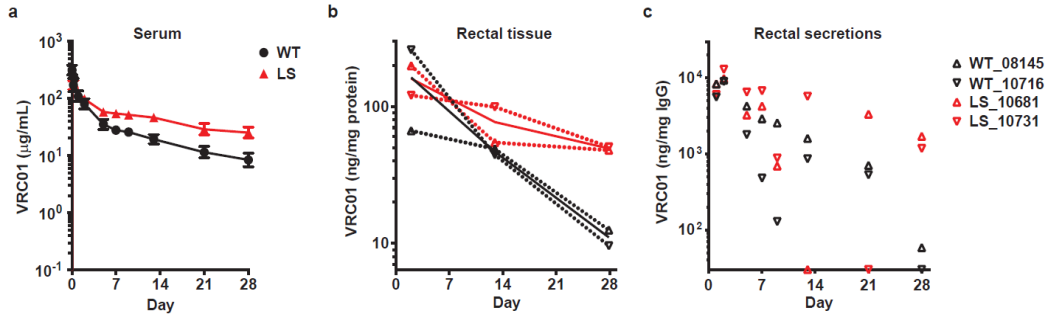

Figure 4-4 Levels of VRC01 (WT) and VRC01LS (LS) in Serum, Rectal Tissues and Rectal Secretions in Cynomolgus Macaques. The values from each monkey and the mean values for the groups are shown as dotted lines and heavier solid lines, respectively.

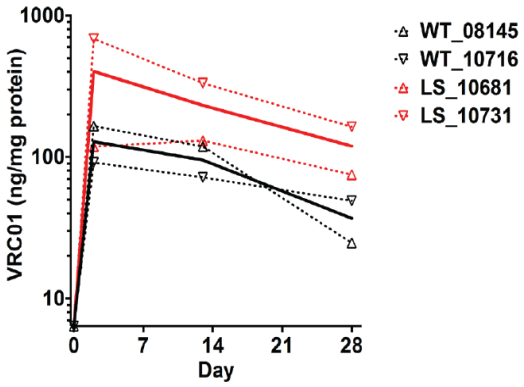

Figure 4-5 Levels of VRC01 (WT) and VRC01LS (LS) in Vaginal Tissue in Cynomolgus Macaques. The values from each monkey and the mean values for the groups are shown as dotted lines and heavier solid lines, respectively.

More information on these studies can be found in the VRC01LS IB.

4.7 Clinical studies

4.7.1 Clinical studies of VRC01

As of March 2016, VRC01 has been tested in HIV-infected adults in the VRC 601 (56) in healthy adults in the VRC 602 (57) and HVTN 104 studies, and in infants born from HIV-1–infected mothers in P1112 (IND 113611). Under IND 126001 in 2015, studies of VRC01 were initiated in HIV-1–infected adults to evaluate the safety and virological effect of VRC01 administration during acute HIV infection (RV398), during a brief analytical treatment interruption (ATI) (A5340) and the effect on the HIV reservoir (A5342). Under IND 126664, a phase 1 study to

evaluate the safety, tolerability, and effect of VRC01 on markers of HIV persistence in ART-treated HIV-infected adults undergoing ATI was initiated. As of February 22, 2018, VRC01 has been administered to over 2600 HIV-uninfected and about 88 HIV-infected adults and about 40 HIV-exposed infants. As of May 10, 2018, no SAEs related to VRC01 have been reported across all studies (communication from DAIDS).

4.7.1.1 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 4-7) 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 4-7 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 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 the remaining 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.

4.7.1.2 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 4-8, 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 4-8 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. Trough levels are shown in Table 4-9 below.

Table 4-9: Trough levels 28 days post first and second infusion

Time	Dose	
	20 mg/kg	40 mg/kg
28 days post infusion #1	35 mcg/ml	57 mcg/ml
28 days post infusion #2	57 mcg/ml	89 mcg/ml

4.7.1.3 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 4-10). 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 4-10 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. Enrollment was completed by July 15, 2015 and infusions were completed November 30, 2015. The study has 5 groups: 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 serum kinetics of *in vitro* neutralization 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 between VRC01 levels and AIA levels in serum; (3) to determine whether measurable levels of VRC01 can be detected in genital, rectal, and oral secretions; (4) to evaluate the kinetics in mucosal secretions of *in vitro* neutralization of a single VRC01-sensitive virus isolate; (5) to assess binding of VRC01 to multiple Env proteins; and (6) to further assess the serum levels of VRC01.

VRC01 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 230 AE's

reported as of February 19, 2016, only 12 (5%), all of them mild, were considered product-related. No SAE/EAEs were reported.

Initial analyses were generated including VRC01 serum levels up to the day 168 visit. The trough level in Group 1 reached an average of 75.6 (64.6, 88.5) ug/ml before the second infusion (day 28), then decreased to trough levels of 50.7 (43, 59.8), 43.4 (36.8, 51.2), 37.3 (26.7, 52.1), and 31.7 (19.9, 50.3), prior to the 3rd (day 56), 4th (day 84), 5th (day 112), and 6th (day 140) infusions, respectively. The last measured level, 28 days after the 6th infusion, was 39.7 (28, 56.3) ug/ml. In Group 2, the trough levels, measured before the second (day 56) and third (day 112) infusions, averaged 20.1 (16.4, 24.6) ug/ml and 21.4 (15.7, 29.2) ug/ml, respectively. The last trough level observation, 28 days after the 3rd infusion, measured 15.1 (6.5, 35.3) ug/ml. In Group 3 (including placebo recipients), the trough levels, measured right before each subsequent 2-weekly SC injection, decreased steadily from 27.7 (8.8, 87.7) ug/ml at day 28 to 8.2 (2.6, 26.3) ug/ml at day 154. The last trough measurement at 14 days after the SC injection was 6 (1.9, 19.3) ug/ml. In Group 4, the trough levels, measured before the second (day 56) and third (day 112) infusions, averaged 4.1 (3.1, 5.3) ug/ml and 2.5 (0.8, 7.9) ug/ml, respectively. The last trough level observation, 28 days after the 3rd infusion, measured 4.2 (1.6, 11.4) ug/ml. In Group 5, the trough levels, measured before the second (day 56) and third (day 112) infusions, averaged 10.4 (6.8, 16.1) ug/ml and 11.5 (7.5, 17.5) ug/ml, respectively. The last trough level observation, 28 days after the 3rd infusion, measured 11.9 (3.8, 38) ug/ml. VRC01 serum levels for Group 4 and Group 5, which use the same doses as HVTN 116, ie VRC01 10mg/kg and 30mg/kg at two month intervals respectively, are shown in Figure 4-6 and Figure 4-7.

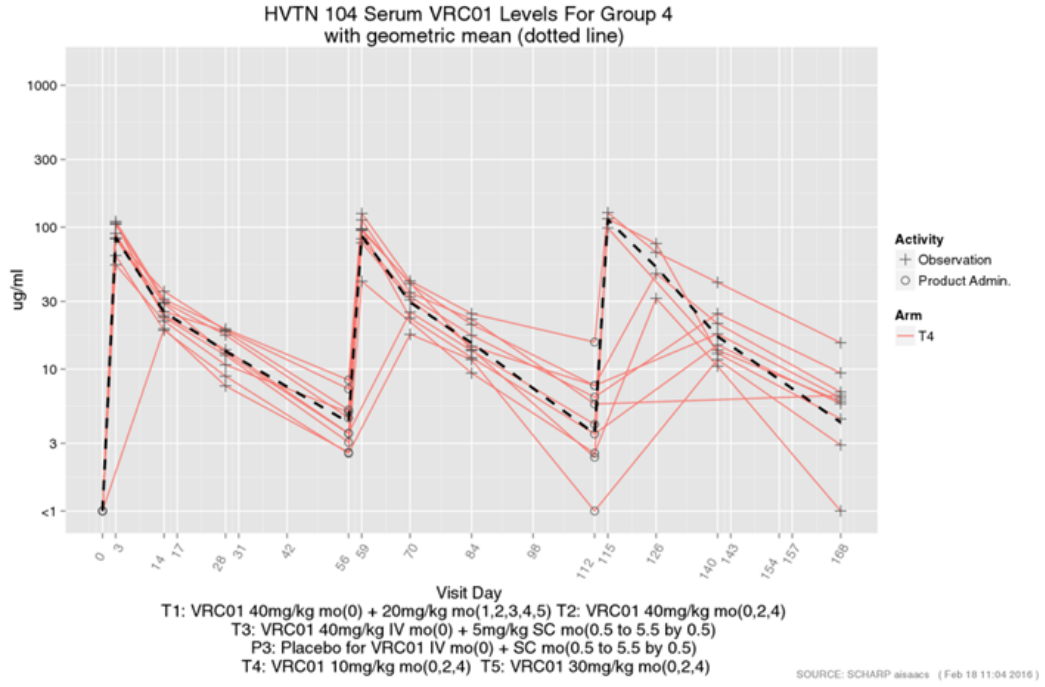

Figure 4-6 VRC01 serum levels in the HVTN 104 per-protocol analysis for Group 4.

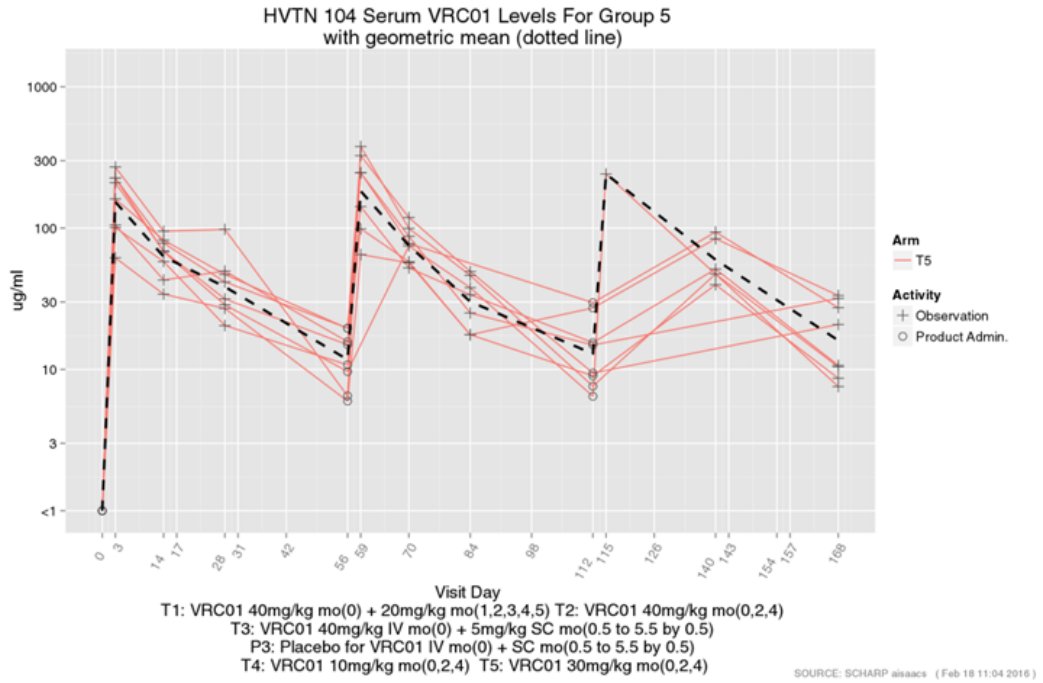

Figure 4-7 VRC01 serum levels in the HVTN 104 per-protocol analysis for Group 5.

4.7.1.4 Safety summary of VRC01

The VRC01 SC administrations were sometimes associated with mild local reactions during the administration that may include some pruritus (itchiness), redness and swelling, which resolves within a few minutes to a few hours after the administration is completed. The largest diameter for erythema or swelling events that were observed during infusions ranged up to about 9 cm. One subject in VRC 602 receiving placebo SC reported mild flushing during administration and one subject in VRC 601 (5 mg/kg SC) reported mild nausea during VRC01 SC administration.

The solicited local and systemic signs and symptoms following administration of VRC01 are generally none to mild. In higher dose groups, 25% of subjects or fewer have reported any moderate or greater solicited reactions after product administration.

There have been no serious adverse events attributed to VRC01 administration. AEs attributed to study product administration on the basis of temporal relationship that did not result in study product discontinuation have included AST, ALT and creatinine elevation, decreased neutrophil count, diarrhea, herpes zoster, and pruritus at the administration site.

In the blinded HVTN 104 trial, there have been three product discontinuations, two in participants receiving subcutaneous administration of VRC01 or placebo and one in the 20mg/kg IV group (Group 1). 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. The discontinuation of the group 1 participant was for an episode of syncope 6 hours after receipt of the third infusion. This incident was deemed not related to study product administration but out of an abundance of caution, the decision was made to withhold the participant's final study drug administration, while continuing safety monitoring visits. In addition, one person in HVTN 104 had study product discontinued due to pregnancy occurring during the trial.

Overall, VRC01 administration in the dose range from 1 to 40 mg/kg IV and at 5 mg/kg SC has been assessed as well-tolerated and safe for further evaluation.

4.7.2 Clinical studies of VRC01LS

VRC01LS is initially being evaluated in the VRC 606 study: "*A Phase 1, Dose-Escalation Study of the Safety and Pharmacokinetics of a Human Monoclonal Antibody, VRC-HIVMAB080-00-AB (VRC01LS), and VRC-HIVMAB060-00-AB (VRC-01), Administered Intravenously or Subcutaneously to Healthy Adults*".

VRC 606 is the first study of the VRC-HIVMAB080-00-AB (VRC01LS) monoclonal antibody (mAb) in healthy adults. It is a dose-escalation study to examine safety, tolerability, dose, and pharmacokinetics of VRC01LS. There are 4 open-label, dose escalation groups (Groups 1-4) to assess VRC01LS administered IV and SC once per subject and 2 open-label groups (Groups 5 and 6) to assess VRC01LS at 5 mg/kg SC or at 20 mg/kg IV administered every 12 weeks for a total of 3 administrations per subject. Two additional open-label groups (Groups 7 and 8) assess VRC01 at 5 mg/kg SC or at 20 mg/kg IV administered every 4 weeks for a total of 2 administrations per subject. The study schema is depicted in Table 4-11.

Table 4-11: VRC 606 Study Schema

Group	Subjects	Product	Administration Schedule			
			Day 0	Week 4	Week 12	Week 24
1	3	VRC01LS	5 mg/kg IV			
2	3	VRC01LS	5 mg/kg SC			
3	3	VRC01LS	20 mg/kg IV			
4	5	VRC01LS	40 mg/kg IV			
5	15	VRC01LS	5 mg/kg SC		5 mg/kg SC	5 mg/kg SC
6	10	VRC01LS	20 mg/kg IV		20 mg/kg IV	20 mg/kg IV
7	5	VRC01	5 mg/kg SC	5 mg/kg SC		
8	5	VRC01	20 mg/kg IV	20 mg/kg IV		
Total*	49					

*Enrollment up to a total of 60 subjects is permitted in case there are subjects who do not complete the schedule, if additional PK evaluations are needed, or if an enrollment of additional subjects is necessary for safety evaluations (Section 4.3).

The first product administration occurred on November 18, 2015 and the study is ongoing. As of July 17, 2017, 39 people have received VRC01LS in three dose groups: 5mg/kg IV and SQ, 20mg/kg IV, and 40mg/kg IV, and 25 participants have completed study participation. No dose limiting toxicities have occurred. There have been no severe adverse events. One participant who received subcutaneous product administration experienced moderate local reactogenicity (pain/tenderness at the injection site). 29 of 39 (74.4%) participants have had one or more unsolicited AEs, with maximum severity of Grade 1 for 18 participants and Grade 2 for 11 participants. Six AEs were assessed as related to study product: two instances of Grade 1 diarrhea, one instance of Grade 1 dizziness, one Grade 1 injection site reaction, and two instances of Grade 1 AST elevation.

VRC01LS administrations have been generally well tolerated.

4.8 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 any 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 generating human anti-mouse antibodies (58). 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, chest pain, or reactions at injection site (pain, redness, bruising, swelling). Clinical use of mAbs that are targeted to cytokines or antigens associated with human cells may be associated with an increased risk of infections (58); 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” (59). “Cytokine release syndrome” and other immune reactions such as tumor lysis syndrome have been observed with administration of chimeric and humanized mAbs (58). 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 (60). 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 (58). 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 (58). 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 (58).

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 However, since 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, in practice this has not been observed in clinical studies with VRC01 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.

Risk of biopsy collections: Possible complications of biopsies are bleeding and infection. These complications are rare and risks of these complications will be minimized by careful hemostasis by the clinicians and detailed education of the participants to report bleeding and/or fever after the procedures. As biopsies create breaches in mucosal integrity, the risk of HIV infection - if exposed - is potentially increased during wound healing. Therefore (and to allow for undisturbed wound healing) an abstinence period is required of the participants (see Section 7.1, Criterion 26 and Section 9.6) after each biopsy. Healing of the superficial wounds in mucous membranes caused by these shallow, small (~2-4mm) biopsies is rapid; by 5-14 days, healing is expected to be complete (61). In the proposed schedule, a minimum of 28 days between biopsy collections will be adhered to, and repetitious biopsies are not assumed to increase the risk as compared to a single biopsy. More than 150 clinic visits involving multiple biopsy collections have been performed at the Seattle HIV Vaccine Trials Unit in the past two years and thus far not a single complication has occurred. In the Cape Town Area Control (CTAC) study, seven female participants were enrolled for the collection of cervical and vaginal samples. Up to five biopsies (cervical, vaginal or a combination of both) were collected at a single visit. Twelve (male and female) participants were enrolled for rectal biopsy collections. To date, two participants underwent first, an anoscopy (with collection of five rectal biopsies), and then a second collection via flexible sigmoidoscopy 10 weeks later (with collection of 5 rectal biopsies and 19 colonic biopsies). Nine participants have undergone one biopsy collection via rigid sigmoidoscopy (with collection of 5 rectal biopsies and 19 colonic biopsies). One participant has undergone two rigid sigmoidoscopies 10 weeks apart (with collection of 5 rectal biopsies and 19 colonic biopsies). All participants were HIV negative at enrollment and have remained HIV negative 1 year post-biopsy collection visit.

In MTN 007, 7 rectal biopsies have been collected three times within one month, respectively, in 65 volunteers. One participant (1.5%) reported grade 1 hematochezia, two participants (3.1%) reported grade 1 painful defecation, and three participants (4.6%) reported grade 1 anal pruritus (62). In a recent phase 1 study of a long-acting antiretroviral, multiple cervical, vaginal, and/or colonic biopsies were collected at baseline and every month for 6 months in 24 female and 12 male participants (ie, 7 collections within a 6-month time frame) with only one significant clinical event related to vaginal biopsies [prolonged bleeding following initial hemostasis that required medical attention but not hospitalization (personal communication Ian McGowan)].

Dr. Susan Cu-Uvin (Brown University), an internationally-recognized expert on gynecological sampling and global health, is currently conducting two different longitudinal biopsy studies that include up to 4 biopsy collection visits (3 cervical and 3 vaginal biopsies at each visit) within a 5-month (healthy women cohort) to 12-month (HIV-infected women cohort) study period. With an overall completion to date of more than 160 cervicovaginal biopsy visits, no biopsy-related complications have been observed.

A review of 34 studies in which 8,330 cervical and vaginal biopsies were taken concluded that there are emerging data that cervical and vaginal biopsies taken among special populations, including women living in high HIV prevalence areas are also safe and well tolerated (63).

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1

- To evaluate the safety and tolerability of VRC01/VRC01LS mAb administered through IV infusion

Primary endpoint 1

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

Primary objective 2

- For each sex at birth, to evaluate the pharmacokinetics of VRC01 in serum versus mucosa in each mucosal compartment

Primary endpoints 2 (Groups 1 & 2 & 4)

- Serum concentration of VRC01 out to Month 6 after the last infusion

- Levels of VRC01 in genital and rectal secretions, as well as cervical, vaginal, and rectal tissues at the collection timepoints

5.2 Secondary objectives and endpoints

Secondary objective 1

- To evaluate the ability of the *in vivo*–infused VRC01/VRC01LS antibodies to inhibit HIV-1 infection in tissue explants

Secondary endpoint 1

- *Ex vivo* inhibition of HIV-1 infectivity in tissue biopsies in Groups 1 - 3

5.3 Exploratory objectives

Exploratory objective 1:

For each sex at birth, to evaluate the pharmacokinetics of VRC01LS in serum versus mucosa in each mucosal compartment

Exploratory objective 2:

To evaluate the levels of VRC01LS in serum, mucosal secretions, and mucosal tissues and those of VRC01 at the 30 mg/kg dose level.

Exploratory objective 3:

To evaluate the tissue distribution of VRC01/VRC01LS in mucosal biopsies.

Exploratory objective 4:

To compare the levels and functionality of VRC01/VRC01LS in mucosal secretions and tissues between the cervical, vaginal, and rectal compartments from the same participant.

Exploratory objective 5:

To assess the relationship between inflammation in mucosal biopsies and levels of antibody in these tissues and related secretions.

Exploratory objective 6:

To assess the acceptability and tolerability of repeat mucosal sampling, including secretions and biopsies, for application in future studies.

Exploratory objective 7:

To assess the relationship between Fc receptor genotypes and VRC01/VRC01LS pharmacokinetics and/or *ex vivo* infectivity of biopsies.

Exploratory objective 8:

To further evaluate the retention of functional characteristics of *in vivo*–infused VRC01/VRC01LS in each group, additional assays may be performed, including on samples from other timepoints.

Exploratory objective 9:

To conduct analyses related to furthering the understanding of HIV, immunology, vaccines, antibody mediated prevention, and clinical trial conduct.

6 Statistical considerations

6.1 Accrual and sample size calculations

Recruitment will target enrolling approximately 74 healthy, HIV-uninfected adult participants into five groups receiving IV administration of either VRC01 or VRC01LS at different schedules and/or dose levels. Groups 1 and 2 participants receive 4 infusions of VRC01 every 2 months at the 10 mg/Kg and 30 mg/Kg dose levels, respectively; Group 3 participants receive 3 infusions of VRC01LS every 3 months at the 30 mg/Kg dose level; Groups 4 and 5 participants receive a single infusion of VRC01 or VRC01LS, respectively, at the 30mg/Kg dose level. Because Groups 1-3 will be enrolled at different sites from Groups 4 and 5, Groups 1-3 were originally randomized with a ratio of 1:1:1, stratified by sex at birth and, separately, Groups 4 and 5 were also originally randomized with a ratio of 1:1 stratified by sex at birth. Groups 3 and 5 will stop enrolling once a minimal number of 12 participants, regardless of sex at birth, are enrolled. At that point, Groups 1 and 2 will be randomized together with a ratio of 1:1, stratified by sex at birth. Groups 1 and 2 will still be enrolled at different sites from Group 4. Groups 1 and 2 (n=23/group) will now be randomized with a ratio of 1:1, stratified by sex at birth. A total of 10 male and 13 female participants will still be enrolled in each of Groups 1 and 2. In Groups 1-3, enrollment is concurrent with the first biopsy procedure(s). In Groups 4-5, enrollment is concurrent with the first infusion. For all groups, randomization occurs prior to the first infusion, ideally within 4 days.

All participants receiving the first complete or partial infusion will provide some safety data. However, for PK analyses of drug levels in serum and mucosa, it is possible that data may be missing for various reasons, such as participants terminating from the study early, or problems in obtaining or shipping specimens. For this reason, the sample size calculations in Section 6.1.2 account for 15% enrolled participants having missing data for the primary lab data endpoint.

6.1.1 Sample size calculations for safety

The goal of the safety evaluation in this study is to identify safety concerns associated with product administration. The ability of the study to detect SAEs can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for a group size of n=16, there is a 90% chance of observing at least 1 event if the true rate of such an event is 13.39% or more; and there is a 90% chance of observing no events if the true rate is 0.64% or less. For a group size of n=23 , there is a 90% chance of observing at least 1 event if the true rate of such an event is 9.52% or more; and there is a 90% chance of observing no events if the true rate is 0.45% or less. For all three VRC01 groups combined (n=62), there is a 90% chance of observing at least 1 event if the true rate of such an event is 3.50% or more; and there is a 90% chance of observing no events if the true rate is 0.16% or less. For both VRC01 groups at the 30 mg/Kg dose level combined (n=39), there is a 90% chance of observing at least 1 event if

the true rate of such an event is 5.72 % or more; and there is a 90% chance of observing no events if the true rate is 0.26 % or less. As a reference, in HVTN vaccine trials from December 2000 through December 2012, about 4% of participants who received placebos experienced an SAE.

Probabilities of observing 0, 1 or more, and 2 or more events among single arms or combined arms of sizes 5, 7, 12, 16, 23, 39, and 62 are presented in Table 6-1 for a range of possible true AE or SAE rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with either VRC01 or VRC01LS (based on the minimal sample sizes).

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among arms of size 5, 7, 12, 16, 23, 39, and 62, for a range of true event rates

True event rate (%)	Group Size	0 Events	1+ Events	2+ Events
1	5	0.95	0.05	<0.01
	7	0.93	0.07	<0.01
	12	0.89	0.11	<0.01
	16	0.85	0.15	0.01
	23	0.79	0.21	0.02
	39	0.68	0.32	0.06
	62	0.54	0.46	0.13
4	5	0.82	0.18	0.01
	7	0.75	0.25	0.03
	12	0.61	0.39	0.08
	16	0.52	0.48	0.13
	23	0.39	0.61	0.23
	39	0.20	0.80	0.47
	62	0.08	0.92	0.71
10	5	0.59	0.41	0.08
	7	0.48	0.52	0.15
	12	0.28	0.72	0.34
	16	0.19	0.81	0.49
	23	0.09	0.91	0.68
	39	0.02	0.98	0.91
	62	<0.01	>0.99	0.99
20	5	0.33	0.67	0.26
	7	0.21	0.79	0.42
	12	0.07	0.93	0.73
	16	0.03	0.97	0.86
	23	<0.01	>0.99	0.96
	39	<0.01	>0.99	>0.99
	62	<0.01	>0.99	>0.99
30	5	0.17	0.83	0.47
	7	0.08	0.92	0.67

	12	0.01	0.99	0.91
	16	<0.01	>0.99	0.97
	23	<0.01	>0.99	>0.99
	39	<0.01	>0.99	>0.99
	62	<0.01	>0.99	>0.99

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the true rate of an adverse event based on the observed data. Table 6-2 shows the 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. Calculations are done using the score test method (64). If none of 16 participants in either of the single infusion groups experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events in the population is 19.36%. If none of 23 participants in Groups 1, 2, or 3 experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events is 14.31%. If none of the 39 participants in the Groups 2+4 experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events is 8.97%. For the total 62 participants in the VRC01 groups, the 95% 2-sided upper confidence bound for this rate is 5.83%.

Table 6-2 Two-sided 95% confidence intervals based on observing a particular rate of safety endpoints for single or combined arms of size 5, 7, 12, 16, 23, 39, and 62

Observed event rate	Confidence interval (%)
0/5	(0.00, 0.43)
1/5	(0.04, 0.62)
2/5	(0.12, 0.77)
0/7	(0.00, 0.35)
1/7	(0.03, 0.51)
2/7	(0.08, 0.64)
0/12	(0.00, 0.24)
1/12	(0.01, 0.35)
2/12	(0.05, 0.45)
0/16	(0.00, 19.36)
1/16	(1.11, 28.33)
2/16	(3.50, 36.02)
0/23	(0.00, 14.31)
1/23	(0.77, 20.99)
2/23	(2.42, 26.80)
0/39	(0.00, 8.97)
1/39	(0.45, 13.18)
2/39	(1.42, 16.89)

0/62	(0.00, 5.83)
1/62	(0.29, 8.59)
2/62	(0.89, 11.02)

6.1.2 Sample size calculations for drug levels

The main goal of this study regarding drug levels involves a preliminary assessment of the correlation between serum and mucosa drug level measurements or corresponding PK parameters estimated after the administration of VRC01 or VRC01LS. The statistical power to detect different levels of correlation (ρ) can be calculated using the Z-transformation (ie, Z'=arctanh(ρ)+ ρ /(2*(n-1)) followed by normal approximation. As shown in Table 6-3, there is limited power (≤ 77%) to detect a correlation of 0.9 or lower in a group size of n=6 or lower. However, for Groups 2+4 (VRC01 30mg/Kg) with n=15 in the assessment of male mucosal compartment, there is approximately 87% power to detect a correlation of 0.7 or higher, and with n = 17 in the assessment of female mucosal compartment, there is approximately 91% power to detect a correlation of 0.7 or higher. For Groups 1+2+4 (VRC01 10mg/Kg or 30 mg/Kg) in the assessment of each mucosal compartment with n=23 in male or n=25 in female, there is >88% or >94% power, respectively, to detect a correlation of 0.6 or higher.

Based on earlier data in non-human primate studies with a total of 12 animals, the observed correlation between log-transformed peak serum and peak mucosa drug levels after a single infusion of VRC01 is in the range of 0.6 to 0.9 (personal communications with VRC colleagues). Therefore, this study is expected to provide reasonable power to achieve the primary objectives regarding drug levels for the combined VRC01 groups if the true correlation between serum and mucosa drug levels is similar to what was observed in the animal studies. There may be a reasonable power (> 77%) to detect correlations between serum and mucosal drug levels in the VRC01LS groups if such data are available from at least 6 participants and the true correlation is at least 0.9.

Table 6-3 Statistical power (%) to detect different levels of correlation between log-transformed serum and mucosal drug levels in group sizes of 6-28 assuming 15% missing data, respectively, in Group 4, Group 1 or 2, Groups 2+4, and Groups 1+2+4 for each

mucosal compartment among males or females (assuming 10 males and 13 females in groups 1 and 2, and 8 males and 8 females in group 4).

True correlation coefficient	Sample size for each mucosal compartment						
	6	**8**	**11**	**15**	**17**	**23**	**28**
0.3	9	11	15	20	22	29	35
0.4	13	17	24	33	37	49	58
0.5	18	25	37	50	56	71	80
0.6	26	37	53	69	76	88	94
0.7	37	53	72	87	91	98	99
0.8	53	73	89	97	99	100	100
0.9	77	93	99	100	100	100	100

6.2 Randomization

The randomization sequence will be obtained by computer-generated random numbers and provided to each HVTN CRS through the SDMC via a Web-based randomization system. Participants will be randomized to either one of Groups 1-3 or one of Groups 4-5, depending on site. The randomization will be stratified by sex at birth and done in blocks to ensure balance. All participants will be randomized prior to the first infusion, ideally within 4 days. Once enrollment has stopped in Groups 3 and 5, participants will then be randomized to either one of Groups 1 and 2 or be enrolled in Group 4, depending on site. At each institution, the pharmacist with primary responsibility for dispensing study products is charged with maintaining consistency of the treatment assignments.

6.3 Blinding

The study will be open label.

6.4 Statistical analysis

This section describes the final study analysis. Of note, Groups 1-3 participants are enrolled 1 month before the first infusion. Groups 4 and 5 participants are enrolled at the first infusion. All analyses pertaining to the safety and drug level objectives of this study are intent-to-treat analyses that include all randomized individuals per their randomization allocation. In addition, analyses will also be performed as treated accounting for the actual infusions and dose levels each participant received.

Analyses will be performed using SAS and R. Other software may be used to perform additional exploratory pharmacokinetics analyses.

No formal multiple comparison adjustments will be employed for multiple safety endpoints.

6.4.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and laboratory measurements for primary- and secondary-objective analyses.

6.4.2 Baseline comparability

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

6.4.3 Safety/tolerability analysis

All participants who received at least 1 partial or complete infusion will provide some safety data.

6.4.3.1 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 infusion visits. In addition, to the individual types of events, the maximum severity of local pain or tenderness, induration or erythema, and of systemic symptoms will be calculated.

6.4.3.2 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.

6.4.3.3 Local laboratory values

Boxplots 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 boxplot will show the first quartile, the median, and the third quartile. Outliers (values outside the boxplot) 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 11.2) will be tabulated by treatment arm for each postinfusion timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will be included in the tabulation of AEs described above.

6.4.3.4 Reasons for discontinuation of study product administration and early study termination

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

6.4.4 Analysis of drug-level endpoints

6.4.4.1 General approach

For the statistical analysis of endpoints, data from enrolled participants will be used according to the initial randomization assignment regardless of how many infusions they received. Additional analyses may be performed, limited to participants who received all scheduled infusions per protocol. Assay results that are unreliable, from specimens collected outside of the visit window, or from HIV-infected participants postinfection will be excluded. Since the exact date of HIV infection is unknown, any assay data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. If an HIV-infected participant does not have a seronegative sample postenrollment, then all data from that participant may be excluded from the analysis.

For continuous assay data (eg, serum concentration of VRC01), graphical and tabular summaries of the distributions by treatment arm and timepoint will be made. Scatterplot matrix with correlation coefficient information between each pair of serum and mucosa drug levels at different timepoints will be provided. An appropriate data transformation (eg, log transformation) may be applied prior to testing to better satisfy analysis assumptions. Inference from these analyses would be limited by the small sample sizes of the groups.

For qualitative assay variables (eg, positive or negative), the analyses will be performed by tabulating the frequency of positive responses for each assay by group at each timepoint at which an assessment is performed. Crude response rates will be presented with their corresponding 95% confidence interval estimates calculated using the score test method (64).

More sophisticated analyses of drug-level data and other assay data collected over time employing repeated measures methodology that is valid under the missing at random (MAR) assumption (for example, nonlinear mixed effects models) may

be utilized to incorporate outcome responses over several timepoints and to account for subject heterogeneity. MAR assumes that the probability of an observation being missing may depend upon the observed responses and upon observed covariates, but not upon any unobserved factors. Generalized nonlinear models for response rates will use a binomial error distribution and for quantitative endpoints, a normal error distribution. All models will include as covariates all available baseline predictors of the missing outcomes.

In addition, non-compartment PK analysis will be performed to estimate PK parameters from individual time-concentration curves. The correlation between individual-level PK parameters estimated for different specimen types (serum vs. mucosa) may also be assessed. All statistical tests will be 2-sided and will be considered statistically significant if $p \leq 0.05$.

For the analysis of correlation between two continuous assay variables over time, graphical summary and tabular summary of the sample correlation at each given timepoint will be made. Cross-correlation of the 2 variables with different time lags may also be calculated and visually displayed if there are at least 10 participants with no missing data over time from both variables. Nonlinear or linear mixed effects models may also be used to predict mucosal drug levels based on serum drug levels collected at the same or previous timepoints. More details of the statistical analysis approaches will be described in a separate Statistical Analysis Plan document.

6.4.5 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, drug level or functional endpoint assessments.

6.4.5.1 Safety

During the course of the trial, analyses of safety data will be prepared approximately every 4 months, as defined in Section 3, for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the PSRT. The HVTN leadership must approve any other requests for safety data prior to the end of the scheduled follow-up visits.

6.4.5.2 Anti-VRC01, anti-VRC01LS and other Laboratory Assessments

Generally, analysis of a primary laboratory endpoint may be performed when all participants have completed the corresponding visit and data are available for analysis from at least 80% of these participants. The Laboratory Program will review the analysis report prior to distribution to the protocol chairs, DAIDS, vaccine developer, and other key HVTN members and investigators. Distribution of reports will be limited to those with a need to know for the purpose of informing future trial-related decisions.

7 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 pharmacokinetics 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 7.1 and 7.2.

7.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 50 years
2. **Weight** ≤ 115 kg
3. **Access to a participating HVTN CRS** and willingness to be followed for the planned duration of the study
4. Ability and willingness to provide **informed consent**
5. **Assessment of understanding**: volunteer demonstrates understanding of this study; completes a questionnaire prior to enrollment with verbal demonstration of understanding of all questionnaire items answered incorrectly
6. **Agrees not to enroll in another study** of an investigational research agent until completion of the last study visit
7. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

8. Willingness to receive **HIV test results**

9. Willingness to discuss HIV infection risks and amenable to HIV risk reduction counseling.

10. Assessed by the clinic staff as being at **"low risk" for HIV infection** [low risk guidelines are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn116)] and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit.

Laboratory Inclusion Values

Hemogram/CBC

11. **Hemoglobin** ≥ 11.0 g/dL for volunteers who were born female, ≥ 13.0 g/dL for volunteers who were born male

12. **White blood cell count** = 2,500 to 12,000 cells/mm^3

13. **Total lymphocyte count** ≥ 800 cells/mm^3

14. **Remaining differential** either within institutional normal range or with site physician approval

15. **Platelets** = 125,000 to 550,000/mm^3

Chemistry

16. **Chemistry panel**: ALT, AST, and alkaline phosphatase < 1.25 times the institutional upper limit of normal; creatinine ≤ institutional upper limit of normal.

Virology

17. **Negative HIV-1 and -2 blood test**: US volunteers must have a negative FDA-approved enzyme immunoassay (EIA). Non-US sites may use locally available assays that have been approved by HVTN Laboratory Operations.

18. **Negative Hepatitis B surface antigen (HBsAg)**

19. **Negative anti-Hepatitis C virus antibodies (anti-HCV)**, or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive

Urine

20. **Normal urine**:

    - Negative urine glucose, and

    - Negative or trace urine protein, and

- Negative or trace urine hemoglobin (if trace hemoglobin is present on dipstick, a microscopic urinalysis with red blood cells levels within institutional normal range).

Reproductive Status

21. **Volunteers who were born female**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test performed prior to initial biopsy for groups 1-3 and prior to initial infusion for groups 4-5 on the day of enrollment. Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

22. **Reproductive status**:

United States

A volunteer who was born female must:

- Agree to consistently use effective contraception (see Appendix C) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit. Effective contraception is defined as using the following methods:
  - Condoms (male or female) with or without a spermicide,
  - Diaphragm or cervical cap with spermicide,
  - Intrauterine device (IUD),
  - Hormonal contraception, or
  - Any other contraceptive method approved by the HVTN 116 PSRT
  - Successful vasectomy in the male partner (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy);
- Or not be of reproductive potential, such as having had a bilateral oophorectomy, or tubal ligation;
- Or be sexually abstinent.

South Africa

A volunteer who was born female must:

- Agree to consistently use effective contraception (see Appendix D) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment

through the last required protocol clinic visit. Effective contraception for participants in South Africa is defined as using 2 methods of birth control.

ONE barrier contraceptive method:

- Condoms (male or female)
- Diaphragm or cervical cap

PLUS ONE of the following methods:

- Intrauterine device (IUD),
- Hormonal contraception, or
- Successful vasectomy in the male partner (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy), or
- Any other contraceptive method approved by the HVTN 116 PSRT

- Or not be of reproductive potential, such as having had a bilateral oophorectomy, or tubal ligation;

- Or be sexually abstinent.

23. **Volunteers who were born female 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

Mucosal Specimen Collection

24. **Volunteers 21 years of age and older who were born female:** Pap smear (verified by medical records) is required within:

    - the 3 years prior to enrollment with the latest result reported as normal or ASCUS (atypical squamous cells of undetermined significance), OR

    - the 5 years prior to enrollment, with the latest result reported as normal, or ASCUS with no evidence of high risk HPV.

    If no Pap smear was done within the last 3 years (or within the last 5 years, if high risk HPV testing was performed), the volunteer must be willing to undergo a Pap smear with the result reported (verified by medical records) as normal or ASCUS prior to sample collection.

25. **Willing to have mucosal secretions and tissue biopsies collected**

26. **Willing to abstain from sexual intercourse for the required period after each biopsy collection**

7.2 Exclusion criteria

General

1. **Blood products** received within 120 days before first infusion, unless eligibility for earlier enrollment is determined by the HVTN 116 PSRT

2. **Investigational research agents** received within 30 days before first infusion

3. **Intent to participate in another study** of an investigational research agent or any other study that requires non-HVTN HIV antibody testing during the planned duration of the HVTN 116 study

4. **Pregnant or breastfeeding**

5. **Active duty US military personnel** with the potential of being deployed during the study

Vaccines and other Injections

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 116 PSRT will determine eligibility on a case-by-case basis.

7. **Non-HIV experimental vaccine(s) received within the last 6 months** in a prior vaccine trial. Exceptions may be made for some vaccines and vaccine trials. For volunteers who have received an experimental vaccine(s) less than 6 months ago, eligibility for enrollment will be determined by the HVTN 116 PSRT on a case-by-case basis.

8. **Live attenuated vaccines** other than influenza vaccine received within 10 days before first Infusion or scheduled within 10 days after first infusion (eg, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever)

9. **Previous receipt of humanized or human mAbs** whether licensed or investigational**.**

Immune System

10. **Immunosuppressive medications** received within 30 days before first infusion. (Not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; or [3] topical corticosteroids for mild, uncomplicated dermatitis)

11. **Serious adverse reactions to VRC01 and VRC01LS 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.

12. **Autoimmune disease** (Not exclusionary: mild, well-controlled psoriasis)

13. **Immunodeficiency**

Clinically significant medical conditions

14. **Untreated or incompletely treated syphilis infection**

15. **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:

    - A process that would affect the immune response,
    - A process that would require medication that affects the immune response,
    - Any contraindication to repeated infusions or blood draws, including perceived inability to establish venous access
    - A condition that requires regular use of any anticoagulant medications (not including aspirin or NSAIDs),
    - 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,
    - A condition or process for which signs or symptoms could be confused with reactions to study product, or
    - Any condition specifically listed among the exclusion criteria below.

16. **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 reactogenicity, or a volunteer's ability to give informed consent

17. **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.

18. **Current anti-tuberculosis (TB) prophylaxis or therapy**

19. **Asthma** other than mild, well-controlled asthma. (Symptoms of asthma severity as defined in the most recent National Asthma Education and Prevention Program (NAEPP) Expert Panel report).

    Exclude a volunteer who:

- Uses a short-acting rescue inhaler (typically a beta 2 agonist) daily, or
- Uses moderate/high dose inhaled corticosteroids, or
- In the past year has either of the following:
  - Greater than 1 exacerbation of symptoms treated with oral/parenteral corticosteroids;
  - Needed emergency care, urgent care, hospitalization, or intubation for asthma.

20. **Diabetes mellitus** type 1 or type 2, including cases controlled with diet alone. (Not excluded: history of isolated gestational diabetes.)

21. **Thyroidectomy, or thyroid disease** unless well controlled (normal T3/T4/TSH) with medication.

22. **Hypertension**:

    - If a person has been found to have elevated blood pressure or hypertension during screening or previously, exclude for blood pressure that is not well controlled. Well-controlled blood pressure is defined as consistently ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic, with or without medication, with only isolated, brief instances of higher readings, which must be ≤ 150 mm Hg systolic and ≤ 100 mm Hg diastolic. For these volunteers, blood pressure must be ≤ 140 mm Hg systolic and ≤ 90 mm Hg diastolic at enrollment.

    - If a person has NOT been found to have elevated blood pressure or hypertension during screening or previously, exclude for systolic blood pressure ≥ 150 mm Hg at enrollment or diastolic blood pressure ≥ 100 mm Hg at enrollment.

23. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)

24. **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)

25. **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.

26. **Asplenia**: any condition resulting in the absence of a functional spleen

27. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema

28. **For those undergoing rectal biopsies, a rectal condition**, such as an active infection or inflammation of the colorectal area (eg, an HSV-2 outbreak or inflamed hemorrhoids or colitis/diarrhea), internal hemorrhoids, or any other condition noted during screening rectal exam via anoscope or in medical history that in the opinion of the clinician represents a contraindication to mucosal sampling.

29. **For those undergoing vaginal and cervical biopsies, any condition** noted during pelvic exam via speculum or in medical history that in the opinion of the clinician represents a contraindication to mucosal sampling.

30. **An active genital tract condition**, such as an active infection or inflammation of the genital tract (eg, genital sores or ulcers, penile or abnormal vaginal discharge, genital warts that are symptomatic or requiring treatment) or any other condition that in the opinion of the clinician represents a contraindication to mucosal sampling.

31. **Hysterectomy**

32. **Menopause**

7.3 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 11.3.

7.3.1 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:

- Within 10 days prior to any infusion
    - Receipt of live attenuated vaccines other than influenza vaccine. The delay may be reduced if residual inflammation from receiving the vaccine has resolved sooner
- Within 14 days prior to any infusion
    - Intercurrent illness that is not expected to resolve prior to the next scheduled infusion which is assessed by the site principal investigator (or designee) to require delay or withdrawal from the infusion schedule. The investigator may consult the HVTN 116 PSRT.
- Pre-infusion abnormal vital signs or clinical symptoms that may mask assessment of study product reaction.

- Pregnancy: for participants who become pregnant, no study product administrations will be given, except for participants who may have been pregnant during the study but are no longer pregnant as shown by 2 negative urine pregnancy tests taken from 2 different urine samples that may be collected on the same day. In this circumstance, the HVTN 116 PSRT should be consulted to determine if the participant may resume study product administrations.

Study product should not be administered outside the visit window period specified in the HVTN 116 Study Specific Procedures.

In order to avoid infusion delays and missed infusions, participants who plan to receive live attenuated licensed vaccines other than influenza vaccine should be counseled to schedule receipt of these substances, when possible, outside the intervals indicated above. The effects of these substances on safety and laboratory assessments and their interactions with study products are unknown.

7.3.2 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, that infusion cannot be given. The participant should resume the infusion schedule with the next infusion unless there are circumstances that require further delay or permanent discontinuation of study product administrations (Sections 7.3.1 and 7.3.3).

7.3.3 Discontinuing study product administrations for a participant

Under certain circumstances, an individual participant's infusions will be permanently or temporarily 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 116 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:
  - Pregnancy (infusions will be stopped while a participant is pregnant. If the participant is no longer pregnant and can be infused within an appropriate visit window, infusions may resume, see Section 7.3.1);
  - HIV infection;
  - Any grade 4 local or systemic reactogenicity symptom, lab abnormality, or AE that is subsequently considered to be related to study product administration;

  - Any grade 3 lab abnormality or other clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to study product administration; or
  - Clinically significant type 1 hypersensitivity reaction associated with study product administration. Consultation with the HVTN 116 PSRT is required prior to subsequent infusions following any type 1 hypersensitivity reaction associated with study product administration; or

- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).

Participants discontinuing study product for reasons other than HIV infection 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.

Participants diagnosed with HIV infection during the study should be encouraged to participate in follow-up visits as indicated in Section 9.14.

7.3.4 Delaying biopsy collections for a participant

An individual participant's biopsy collections may be delayed in certain circumstances as described in section 9.6. Apart from medical reasons (eg, menstruation or infection), personal reasons may also trigger such delays. If biopsy collection is delayed, it should be performed as soon as possible, within the visit window. Biopsies should not be performed outside the visit windows specified in the HVTN 116 Study Specific Procedure. The participant should resume the biopsy collection schedule with the next biopsy collection unless there are circumstances that require further delay or permanent discontinuation of biopsy collections (see section 7.3.5).

Pregnancy: for participants who become pregnant, no biopsies will be collected, except for participants who may have been pregnant during the study but are no longer pregnant as shown by 2 negative urine pregnancy tests taken from 2 different urine samples that may be collected on the same day. In this circumstance, the HVTN 116 PSRT should be consulted to determine if the participant may resume biopsy collection.

7.3.5 Discontinuing biopsy collections for a participant

An individual participant's biopsy collections will be permanently discontinued under certain circumstances, including:

- Increase in risk of HIV infection, as indicated by:
  - New diagnosis of chlamydia, gonorrhea, syphilis, or any other disease that, in the clinician's opinion may indicate an increased risk of HIV infection

  - Change in HIV risk behavior

- HIV infection

- Any medical condition that presents a contraindication for biopsies (eg, a condition requiring anticoagulants), in consultation with the PSRT

- Investigator determination in consultation with the PSRT and/or Protocol Team leadership (this may include, but is not limited to, situations in which no tissue Ab levels were detected at a previous visit)

- The participant is no longer willing to provide biopsies

7.3.6 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 HVTN CRS is not possible,

- HVTN CRS determines that the participant is lost to follow-up, or

- 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.

- Participant declines further mucosal biopsies between the baseline biopsies and the first infusion (Groups 1-3).

If study product is not detectable in any of the samples (including biopsies) at two consecutive follow-up visits, participants may be excluded from further sample collections at the discretion of the HVTN 116 PSRT. If such a decision is reached, the participant will be terminated after a final study visit.

8 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 3-1.

See the Investigator's Brochures for further information about study products.

8.1 Infusion regimen

The schedule of infusions is shown in Section 3 and additional information is given below. The study is open label.

Group 1

Treatment 1 (T1): VRC01 (VRC-HIVMAB060-00-AB) 10 mg/kg to be administered IV in 100 mL of Sodium Chloride for Injection USP, 0.9% at Month 0, Month 2, Month 4, and Month 6.

Group 2

Treatment 2 (T2): VRC01 (VRC-HIVMAB060-00-AB) 30 mg/kg to be administered IV in 100 mL of Sodium Chloride for Injection USP, 0.9% at Month 0, Month 2, Month 4, and Month 6

Group 3

Treatment 3 (T3): VRC01LS (VRC-HIVMAB080-00-AB) 30 mg/kg to be administered IV in 100 mL of Sodium Chloride for Injection USP, 0.9% at Month 0, Month 3, and Month 6

Group 4

Treatment 4 (T4): VRC01 (VRC-HIVMAB060-00-AB) 30 mg/kg to be administered IV in 100 mL of Sodium Chloride for Injection USP, 0.9% at Month 0.

Group 5

Treatment 5 (T5): VRC01LS (VRC-HIVMAB080-00-AB)30 mg/kg to be administered IV in 100 mL of Sodium Chloride for Injection USP, 0.9% at Month 0.

8.2 Study product formulation

VRC01 (Labeled as VRC01 HIV MAb Drug Product VRC-HIVMAB060-00-AB)

VRC01 will be supplied at a concentration of 100 ± 10 mg/mL in an isotonic, sterile solution. Two fill volumes are available: 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 ± 0.1 mL fill volume. The vials contain a clear, colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 25 mM sodium citrate, 50 mM sodium chloride, and 150 mM L-arginine hydrochloride at pH 5.8. The vials are intended for single use only and thus do not contain a preservative.

VRC01 product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F). Clinical site storage in a continuously monitored, temperature-controlled freezer with temperature excursions between -45°C to -10°C (-49°F to 14°F) is acceptable.

VRC01LS (Labeled as VRC01LS HIV MAb Drug Product VRC-HIVMAB080-00-AB)

VRC01LS will be supplied in 10 mL glass vials with a 6.25 ± 0.1 mL fill volume at a concentration of 100 ± 10 mg/mL and 3 mL glass vials with a 2.25 + 0.1 mL fill volume. The vials contain a clear, colorless to yellow liquid essentially free of visible particles; some opaque or translucent particles may be present. 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 thus do not contain a preservative.

VRC01LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F). Clinical site storage in a continuously monitored, temperature-controlled freezer with temperature excursions between -45°C to -10°C (-49°F to 14°F) is acceptable.

8.3 Preparation of study products

8.3.1 VRC01 (T1, T2, T4)

Thawing instructions

Thaw vials of VRC01 at controlled room temperature (maximum 27ºC) for a minimum of 1 hour. Thawed vials should contain fluid that is a clear, colorless to yellow liquid essentially free of visible particles. VRC01 vials must either be used to prepare an infusion or placed in a refrigerator at 2°C to 8°C (36°F to 46°F)

before reaching the maximum storage of 24 hours at room temperature; VCR01 may be stored up to 4 weeks at 2°C to 8°C (36°F to 46°F).

VRC01 may not be stored in direct sunlight at anytime.

VRC01 is a highly concentrated protein solution and may develop white, opaque-to-translucent particles after thawing. Vial(s) of VRC01 containing particles should be placed in the refrigerator as particles may continue to dissipate at 2-8°C. Vials of VRC01 that previously contained particles but subsequently become clear of particles may be used. Vials that continue to have visible particles after a maximum of 4 weeks at 2°C to 8°C (36°F to 46°F) are not to be used and will be discarded in a biohazard containment bag and incinerated or destroyed in accordance with institutional or pharmacy policy. Report to the protocol pharmacist the quantity and the reason why for the disposal of any unused vials.

IV infusion preparation instructions

The pharmacist must receive a prescription that states the participant's weight obtained at the most recent visit where weight was measured. Participants' screening weight, entry weight, or last obtained weight may be used for estimating the dose to thaw vials. After removal from 2-8°C, vials of VRC01 must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes prior to preparing IV infusions. The maximum length of time that VRC01 in the vial may be held at controlled room temperature (maximum 27°C) prior to product preparation is 8 hours after removal from the refrigerator.

Prior to preparation for administration, vials should be swirled for 30 seconds with sufficient force to resuspend any visible particles, yet avoiding foaming. DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage. If particles continue to be observed, do not use the vialed product for IV administration. If the particles redissolve within the maximum storage times of up to 4 weeks at 2°C to 8°C, the vials may be used for product preparation.

1. Calculate the total milligrams of VRC01 required based on the participants weight and the randomized treatment group of either 10 mg/kg or 30 mg/kg and the total number of vials required based on a 6 mL withdrawal volume containing 600 mg of VRC01 or 2 ml withdrawal volume containing 200 mg of VRC01.

2. Gently swirl thawed vials for 30 seconds, yet avoiding foaming. DO NOT SHAKE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vial during inspection.

3. Observe vials for particles. If particles are observed refer to the thawing instructions for further information.

4. Add the required volume for the calculated total milligrams needed to 0.9% Sodium Chloride for Injection, USP 100 mL IV bag or IV glass bottle using aseptic technique to maintain sterility in a clean room with limited access using either an isolator, laminar flow hood, or biological safety cabinet following the country's requirements for medium risk sterile compounding. The 0.9% Sodium Chloride for Injection, USP, 100 mL bag will accommodate the additional volume required for the dose of VRC01 to be used in this study. Do not withdraw fluid from the 0.9% Sodium Chloride Injection, USP, 100 mL bag to make room for the volume of study product to be added. Alternatively, the pharmacist can obtain a different volume of 0.9% Sodium Chloride for Injection, USP (50 ml, 150 mg, 200 mg, 250 ml, 500 ml, etc.) for use to prepare the study IV infusion in 100 mls of 0.9% Sodium Chloride for Injection, USP.

5. Label the IV bag with patient identifier, the randomized dose of VRC01 of either 10mg/kg or 30 mg/kg, and the total amount (mg) of VRC01 added to the 0.9% Sodium Chloride Injection, USP, 100 mL, the final volume of the bag, lot number, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

After product preparation in IV bags, the prepared VRC01 may be stored at 2°C to 8°C up to 96 hours or at room temperature (maximum 27°C) for a maximum of 6 hours total including the infusion.

The IV bag will also be labeled with a DO NOT INFUSE after date and time as follows:

- 96 hours if stored at 2°C to 8°C
- 6 hours, including completion of infusion, if at room temperature (maximum 27°C).

Any unused portion of a VRC01 vial will not be used for another participant. Any empty vials, unused portion of entered vials, or unused IV solution which contains study product should be discarded in a biohazard containment bag and incinerated or destroyed in accordance with institutional or pharmacy policy.

8.3.2 VRC01LS (T3, T5)

Thawing instructions

Thaw vials of VRC01LS at controlled room temperature (maximum 27°C) for a minimum of 1 hour after removing from freezer. Thawed vials should contain fluid that is a clear, colorless to yellow liquid and no particles are observed. VRC01LS vials must either be used to prepare an infusion or placed in a refrigerator at 2°C to 8°C (36°F to 46°F) before reaching the maximum storage of

24 hours at controlled room temperature (maximum 27°C); VCR01LS may be stored up to 4 weeks at 2°C to 8°C (36°F to 46°F).

If stored at 2°C to 8°C (36°F to 46°F), vials must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes and may be held at controlled room temperature (maximum 27°C) for up to 8 hours prior to product preparation.

VRC01LS may not be stored in direct sunlight at anytime.

VRC01LS is a highly concentrated protein solution and may develop white, opaque-to-translucent particles after thawing. Vial(s) of VRC01LS containing particles should be placed in the refrigerator as particles may continue to dissipate at 2-8°C. Vials of VRC01LS that previously contained particles but subsequently become clear of particles may be used.

Vials that continue to have visible particles after a maximum of 4 weeks at 2°C to 8°C (36°F to 46°F) are not to be used and will be quarantined and continued to be stored at 2°C to 8°C (36°F to 46°F.) Contact the protocol pharmacist for further instructions regarding handling of vials of VRC01LS with particles.

IV infusion preparation instructions

The pharmacist must receive a prescription that states the participant's weight obtained at the most recent visit where weight was measured. Participants' screening weight, entry weight, or last obtained weight may be used for estimating the dose to thaw vials. After removal from 2-8°C, vials of VRC01LS must be equilibrated to controlled room temperature (maximum 27°C) for a minimum of 30 minutes prior to preparing IV infusions.

1. Calculate the total milligrams of VRC01LS required based on the participants weight, 30 mg/kg and the total number of vials required based on a 6 mL withdrawal volume containing 600 mg of VRC01LS or 2 ml withdrawal volume containing 200 mg of VRC01LS.

2. Gently swirl thawed vials for 30 seconds, yet avoiding foaming. DO NOT SHAKE VIALS. Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vial during inspection.

3. Observe vials for particles. If particles are observed refer to the thawing instructions for further information.

4. Add the required volume for the calculated total milligrams needed to 0.9% Sodium Chloride for Injection, USP 100 mL IV bag or glass bottle using aseptic technique to maintain sterility in a clean room with limited access using either an isolator, laminar flow hood, or biological safety cabinet following the country's requirements for medium risk sterile compounding. The 0.9% Sodium Chloride for Injection, USP, 100 mL bag

will accommodate the additional volume required for the dose of VRC01LS to be used in this study. Do not withdraw fluid from the 0.9% Sodium Chloride for Injection, USP, 100 mL bag to make room for the volume of study product to be added. Alternatively, the pharmacist can obtain a different volume of 0.9% Sodium Chloride for Injection, USP (50 ml, 150 mg, 200 mg, 250 ml, 500 ml, etc.) for use to prepare the study IV infusion in 100 mls of 0.9% Sodium Chloride for Injection, USP.

5. Label the IV bag with patient identifier, dose of VRC01LS 30 mg/kg, and the total amount (mg) of VRC01LS added to the 0.9% Sodium Chloride Injection, USP, 100 mL, the final volume of the bag, lot number, storage instructions, Investigational Use Statement ("Limited by Federal Law to Investigational Use"), and manufacturer information.

After product preparation in IV bags, the prepared VRC01LS may be stored at 2°C to 8°C (36°F to 46°F) up to 24 hours or at room temperature (maximum 30°C) for a maximum of 8 hours total including infusion time.

The IV bag will also be labeled with a DO NOT INFUSE after date and time as follows:

- 24 hours if stored at 2°C to 8°C
- 8 hours, including completion of infusion, if at room temperature (maximum 30°C).

Any unused portion of a VRC01LS vial will not be used for another participant. Any empty vials, unused portion of entered vials, or unused IV solution which contains study product should be discarded in a biohazard containment bag and incinerated or destroyed in accordance with institutional or pharmacy policy.

8.4 Administration

VRC01 and VRC01LS (intravenously)

An in-line filter infusion set must be used for IV administration (see the HVTN 116 SSP for specifications and additional details). In-line filters must comply with the following specifications: 1.2 micron PES (polyethersulfone) filter membrane, DEHP-free, latex-free (equivalent to Braun #473994 filter extension set). When the in-line filter is added to the tubing, prime the administration set. Flush the administration set with about 30 mL or appropriate volume of normal saline at the end of product administration.

For Groups T1, T2, T3, T4, and T5: The IV bag prepared by the pharmacy will include the total amount (mg) of VRC01 or VRC01LS added to the 100 mL normal saline bag and the final volume of the bag. The clinician responsible for administration and another clinician will each check the bag label and confirm

that the identifier is correct and that the correct total milligrams to be administered is shown based on subject weight and dosage level before beginning the IV administration. The investigational study product solution will typically be administered IV over about 15 to 60 minutes using a volumetric pump. The rate of infusion (mL/hr) will vary based on the total volume needed to administer the full dose. The total time needed to administer the dose may be longer based on factors such as subject tolerance.

8.5 Acquisition of study products

VRC01 (VRC-HIVMAB060-00-AB) and VRC01LS (VRC-HIVMAB080-00-AB) are provided by the VRC/DAIDS/NIAID.

Once an HVTN 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.

8.6 Pharmacy records

The HVTN 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.

8.7 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.

9 Clinical procedures

The schedules of clinical procedures are shown in Appendix L, Appendix M, Appendix N, and Appendix O.

9.1 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 HVTN 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 an HVTN study. Informed consent encompasses all written or verbal study information HVTN CRS staff provide to the participant, before and during the trial. HVTN CRS staff will obtain informed consent of participants according to HVTN 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, HVTN 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.

An HVTN CRS may employ recruitment efforts prior to the participant consenting. For example, some HVTN 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. HVTN CRSs must submit recruitment and prescreening materials to IRB/EC and any applicable Regulatory Entity (RE) for human subjects protection review and approval.

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

9.1.1 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 HVTN 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 vaccine or other prevention trial. In this way, HVTN 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 periods specified in the eligibility criteria.

9.1.2 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 study is located in Appendix A for Groups 1-3 and Appendix B for Groups 4-5. A separate sample consent form for other uses of specimens is located in Appendix E for all groups.

Each HVTN 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 for Groups 1-3 and Appendix B for Groups 4-5. The consent form(s) must be developed in accordance with requirements of the following:

- CRS's IRB/EC,
- CRS's institution and any applicable REs, 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.

9.1.3 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 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.

9.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before baseline biopsy collection on day -14 (Groups 1-3), or infusion on day 0 (Groups 4 and 5). All inclusion and exclusion criteria must be assessed within 56 days before enrollment, 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;
- Assessment of whether the volunteer is at low risk for HIV infection;
- 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; skin; and pelvic and/or rectal exam;
- 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);
- Pap smear (only for volunteers 21 years or older who were born female and who did not have a Pap smear performed within the last 3-5 years; for specific requirements see Section 7.1, Criterion 24)

- Specimen collection (including mucosal sampling as described in Section 9.6, for groups 4 and 5)

- Laboratory tests, including:
  - Complete Blood Count including differential and platelets
  - ALT, AST, AP, and Creatinine
  - Urine or serum pregnancy test (for participants who were born female). Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
  - Urine dipstick (Urinalysis if indicated)
  - Screening HIV testing
  - Hepatitis B and C
  - Syphilis
  - Gonorrhea and chlamydia
  - Trichomonas vaginalis (for participants providing cervicovaginal samples),
  - Bacterial vaginosis (for participants providing cervicovaginal samples),
  - Yeast (for participants providing cervical samples, if clinically indicated),

- Administration of behavioral risk assessment questionnaire;

- Obtaining 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 the US Centers for Disease Control and Prevention (CDC)'s current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 9.7; 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 study inclusion criteria. 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.

9.2.1 Use of screening results from another HVTN study

If a participant screens for an HVTN study at the same HVTN 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 (Sections 7.1 and 7.2).

9.3 Enrollment visits

Enrollment in Groups 1, 2, and 3 is simultaneous with baseline biopsy collections on day -14. Enrollment in Groups 4 and 5 is simultaneous with the infusion on day 0. The time interval between randomization and first infusion should not exceed 4 working days. The CRS requests the randomization assignment from the Web-based randomization system. Randomization will be performed prior to first infusion for all groups.

At the baseline biopsy collection visit (Groups 1-3; day -14), cervical, vaginal, and/or rectal biopsies will be collected. These samples will serve as baseline controls and will help to assess the acceptability of the biopsy procedures to participants and the fitness of participants to continue in these groups with extensive mucosal biopsy collections. Participants with conditions not amenable to repeated biopsy sampling or participants not willing to continue in the trial after these baseline biopsies have been performed may be replaced.

At the baseline biopsy collection visit (Groups 1-3; day -14), the following procedures are performed:

- 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
- Assessment of concomitant medications (Section 9.2)
- Assessment of any new or unresolved AEs/intercurrent illnesses
- Urine or serum pregnancy test (for participants who were born female). Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing
- Risk reduction counseling (Section 9.7)
- Pregnancy prevention assessment (Section 9.2 and 9.8)

- 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)
- Specimen collection (including mucosal sampling as described in Section 9.6);
- HSV 1/2 testing
- Blood hormone levels (estradiol and progesterone) (persons born female only)
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate.

For the enrollment infusion visit (Groups 4 and 5; day 0) procedures are described in Section 9.4.

9.4 Infusion visits

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;
- Assessment of baseline reactogenicity parameters;
- Assessment of concomitant medications (Section 9.2);
- Assessment of any new or unresolved AEs/intercurrent illnesses; and
- Urine or serum pregnancy test (for participants who were born female). Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;
- Blood collection for serum trough levels and storage (not applicable at the first infusion visit in Groups 1-3, as baseline samples will be collected at enrollment).

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (Sections 8.3 and 8.4).

Immediately following infusion, the participant remains in the clinic for observation. An initial reactogenicity assessment is made at a target of 30 minutes after all IV infusions, with an acceptable range of 25-60 minutes. Before leaving

the clinic, the participant is given the postinfusion memory tool and is instructed on how to complete it. The site will make arrangements to obtain daily reports of reactogenicity events from the participant during the reactogenicity period (Section 9.10).

The following procedures will be performed at infusion visits as specified in Appendix L, Appendix M, Appendix N, and Appendix O. These procedures may be performed prior to, during, or following infusion:

- Risk reduction counseling (Section 9.7);
- Pregnancy prevention assessment (Section 9.2 and 9.8); and
- 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 the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
- Administration of behavioral risk assessment questionnaire;
- Biopsy acceptability questionnaire;
- HSV 1/2 testing
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate.

9.5 Follow-up visits

The following procedures are performed at all scheduled follow-up visits:

- Risk reduction counseling (Section 9.7);
- Pregnancy prevention assessment (Section 9.2 and 9.8); and
- 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);
- Assessment of new or continuing concomitant medications (Section 9.2); and
- Assessment of new or unresolved AEs/intercurrent illnesses.

Additional procedures will be performed at scheduled follow-up visits as specified in in Appendix L, Appendix M, Appendix N, and Appendix O:

- Administration of the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
- Administration of behavioral risk assessment questionnaire;
- Biopsy acceptability questionnaire;
- 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;
- 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;
- 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;
- Specimen collection (including mucosal sampling as described in Section 9.6);
- Clinical laboratory tests including:
  - CBC with differential and platelets,
  - Chemistry panel (Section 9.2),
  - Blood hormone levels (estradiol and progesterone) (persons born female only),
  - Urine dipstick (urinalysis if appropriate; Section 9.9),
  - Gonorrhea and chlamydia,
  - Trichomonas vaginalis,
  - Bacterial vaginosis,
  - Yeast (if clinically indicated).
- Urine or serum pregnancy test (for participants who were born female). Persons who are NOT of reproductive potential due to having undergone

bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

9.6 Mucosal sampling

Mucosal secretion and biopsy samples will be collected at the timepoints indicated in Appendix L, Appendix M, Appendix N, and Appendix O. All participants in this trial will have consented to mucosal specimen collections. Participants born male will provide semen, rectal fluids, and rectal biopsies. Participants born female will provide cervicovaginal fluids, as well as cervical and vaginal biopsies. At the Seattle CRS, female participants will also provide rectal fluids and rectal biopsies, if they agree to do so. Small (~2-4 mm) tissue biopsies are obtained from the vagina and cervix using a speculum and from the rectum by anoscopy by experienced clinicians. The number of biopsies per mucosal compartment and visit is described in detail in Table 9-1 and Table 9-2, and also outlined in Appendix H, Appendix I, Appendix J, and Appendix K, however fewer samples may be taken based on the judgment of the performing clinician. If a female participant is no longer willing to provide cervicovaginal specimens, a switch to the rectal compartment is possible. During the trial, a participant may decline all or some of the mucosal biopsies or secretion collections, but they should be encouraged to continue with any collections that they deem acceptable until the end of the trial.

Table 9-1 Mucosal biopsy collection schedule for Groups 1-3

Tissue	Function	Visit 2 (Baseline)	Visit 14 (Month 6)	Visit 15 (Month 7)	Visit 16 (Month 9)	Visit 17 (Month 12)	Visit 18** (Month 15)	Visit 19** (Month 18)
Rectal # of Bx and Use	Ab levels	1	1	1	1	1	1	1
	IHC	1	1	1	1	1	1	1
	Infectivity	3	3	3	3	3	3	3
	Total = 35*/25	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Ectocervical # of Bx and Use	Ab levels	1	1	1	1	1	1	(1)***
	IHC	1	1	1	1	1	1	(1)***
	Infectivity	2	2	-	-	-	-	-
	Total = 16*/14	**4**	**4**	**2**	**2**	**2**	**2**	**(2)*****
Vaginal # of Bx and Use	Ab levels	1	1	1	1	1	1	(1)***
	IHC	1	1	1	1	1	1	(1)***
	Infectivity	3	3	3	3	(3)***	(2-3)***	(2-3)***
	Total = 24*/22	**5**	**5**	**5**	**5**	**2 [(5)***]**	**2 [(4-5)***]**	**(2-5)*****

* Number of samples refers to Group 3
** Visits only apply to group 3
*** These samples will only be collected if the participant has missed prior collection visit(s), in order to maintain the total number of biopsies indicated in the "Function" column.

Table 9-2 Mucosal biopsy collection schedule for Groups 4-5

Tissue	Function	Visit 4 (0 mo)	Visit 5 (1 mo)	Visit 9 (3 mo)	Visit 12 (4.5 mo)	Visit 14 (6 mo)	Visit 16** (9 mo)	Visit 17** (12 mo)
Rectal # of Bx and Use	Ab levels	1	1	2	2	1	2	1
	IHC	1	1	-	-	1	-	1
	Infectivity	-	-	-	-	-	-	-
	Total = 14*/10	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Ectocervical # of Bx and Use	Ab levels	1	1	2	2	1	2	1
	IHC	1	1	-	-	1	-	1
	Infectivity	-	-	-	-	-	-	-
	Total = 14*/10	**2**	**2**	**2**	**2**	**2**	**2**	**2**
Vaginal # of Bx and Use	Ab levels	1	1	2	2	1	2	1
	IHC	1	1	-	-	1	-	1
	Infectivity	-	-	-	-	-	-	-
	Total = 14*/10	**2**	**2**	**2**	**2**	**2**	**2**	**2**

* Number of samples refers to Group 5
** Visits only apply to group 5

- At each biopsy visit, prior to biopsy, participants must be confirmed to be low-risk for HIV infection.

- Participants will regularly be tested for gonorrhea and chlamydia. Additionally, participants who were born female will be tested for trichomoniasis and bacterial vaginosis and may be tested for hyphae/budding yeast (if clinically indicated) as outlined in Appendix L, Appendix M, Appendix N, and Appendix O. In addition to the pre-defined testing timepoints, such tests may be performed at any time according to the clinicians' discretion. Test results will be provided to participants and all participants who test positive for 1 or more of these infections will receive counseling, as well as treatment or referral for treatment as appropriate. Sample collection will not be performed or may be deferred to a later date within the visit window if a contraindication to sampling (eg, active GTI) is present (as indicated below).

- Rectal fluid and/or biopsy sampling. For participants born female and capable of becoming pregnant, a pregnancy test must be performed and be negative prior to any rectal mucosal sampling. Participants should abstain from receptive anal sex, insertion of any foreign object or substance into the anus (including but not limited to cleaning products [creams, gels, lotions, pads, etc.], lubricant, enemas, and douching even with water), and using perianal or intra-anal steroid or other anti-inflammatory cream in or around the anus for 48 hours prior to sample collection. Rectal secretion sampling may be deferred if a participant is menstruating, but should be performed as soon as possible, within the visit window. In addition, rectal sampling will not be

performed (or may be deferred to a later date within the visit window) if there is a contraindication to rectal secretion sampling, such as an active infection or inflammation of the colorectal area (such as an HSV-2 outbreak or inflamed hemorrhoids or colitis/diarrhea).

- Additional biopsy-specific criteria:
  - Biopsies will be collected a minimum of 28 days from previous biopsies.
  - Participants should not have taken antithrombotic medication (except ASA and NSAIDs) for 5 days prior to the procedure. If a participant is taking these medications for medical reasons, biopsies should not be collected and these medications should not be interrupted.
  - Participants should not have rectal sex and/or insert any foreign object or substance into the rectum for **5 days after** biopsy samples have been collected;
  - Participants should contact the clinic if they experience a large amount of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not improving.

- Cervicovaginal secretion and/or biopsy sampling. Participants who are age 21 or older must report having had a Pap smear within the 5 years prior to enrollment, with the latest result reported as normal, or ASCUS (atypical squamous cells of undetermined significance) with no evidence of high-risk HPV; if high-risk HPV testing was not conducted, the participant must report having had a Pap smear within the 3 years prior to enrollment, with the latest result reported as normal or ASCUS. Pap smear results must be verified by medical records. For participants capable of becoming pregnant, a pregnancy test must be performed and must be negative prior to any cervicovaginal mucosal sampling with a sponge. For sampling with menstrual cup, the pregnancy test can be performed after collection has taken place, but should be performed on the same day as the collection. Cervicovaginal mucosal sampling should be deferred if a participant is menstruating, but should be performed as soon as possible, within the visit window. If this is not possible, cervicovaginal biopsies may be collected within the visit window during menses at the clinician's discretion. In addition, cervicovaginal sampling will not be performed (or may be deferred to a later date within the visit window) if a participant has an active ulcerative genital lesion or is known to have an active GTI at the scheduled timepoint. Participants providing cervicovaginal samples should be advised as follows:
  - Do not use anything with spermicide, lubricants, or topical/intravaginal medications (eg, topical yeast infection treatments) for 48 hours before the samples are collected;
  - Do not douche for 48 hours before the samples are collected;

- Do not have vaginal sex and/or insert any foreign object or substance into the vagina for 48 hours before the samples are collected;

- Additional biopsy-specific criteria:

  - Biopsies will be collected a minimum of 28 days from previous biopsies.

  - Participants should not have taken antithrombotic medication (except ASA and NSAIDs) for 5 days prior to the procedure. If a participant is taking these medications for medical reasons, biopsies should not be collected and these medications should not be interrupted.

  - Participants should not have vaginal sex and/or insert any foreign object or substance into the vagina for **7 days after** biopsy samples have been collected;

  - Participants should contact the clinic if they experience a large amount of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not improving.

- Semen sampling. Participants providing semen samples are asked to refrain from ejaculation, using anything with lubricants, putting saliva on the penis, or having receptive oral sex for at least 48 hours prior to specimen collection. In addition, semen sampling will not be performed (or may be deferred to a later date within the visit window) if a participant is known to have an active GTI at the scheduled timepoint.

9.7 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 current HVTN HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection.

Potential participants identified as being HIV infected during screening are not enrolled. Potential and enrolled participants identified as being HIV-infected will be referred for medical treatment, counseling, and management of the HIV infection. Participants who are found to be HIV-infected after enrollment will not receive any additional study product but will continue to be followed in the study for safety assessments. These individuals may also be referred to appropriate ongoing clinical trials or observational studies.

It is theoretically possible that anti-HIV mAb administration may cause common antibody tests to show that someone is HIV-negative, even if they are actually infected. An anti-HIV mAb is not likely to directly reduce or inhibit the assays used to detect HIV-1 infection.

9.7.1 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/VRC01LS 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 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/VRC01LS causing a misleading HIV test result will disappear before their final scheduled clinic visit.

9.8 Contraception status

Contraception status is assessed and documented at every scheduled clinic visit for a participant who was born female and who is sexually active in a way that could cause that participant to become pregnant. Prior to enrollment and throughout the study, staff will ask participants to verbally confirm their use of adequate contraceptive methods. A participant who was born female and is sexually active in a way that could cause that participant to become pregnant should be reminded at all scheduled clinic visits of the importance of using contraception and should be referred to specific counseling, information, and advice as needed. (Specific contraception requirements are listed in Section 7.1). This reminder should be documented in the participant's study record.

Self-reported infertility—including having undergone bilateral oophorectomy or tubal ligation—must be documented in the participant's study record.

9.9 Urinalysis

Dipstick testing may be performed in the clinic or the lab, as long as the required elements (glucose, protein, and hemoglobin) are tested. The examination is performed on urine obtained by clean catch.

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

Follow-up urinalysis should be deferred if a participant is experiencing non-urinary bleeding (eg, 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 case report form (CRF) and repeat the dipstick once the participant is no longer menstruating. A micro-urinalysis is not required.

9.10 Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after infusions per SSP. All reactogenicity symptoms are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, except as noted in Section 11.2.2.

The reactogenicity assessment period is 3 full days following each infusion per the assessment schedule shown in Table 9-3. Participants are instructed to record symptoms using a postinfusion memory tool. Contacts between the participant and the site staff should take place daily during the assessment period. 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 infusions 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 in Table 9-3. 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 event log form.

Table 9-3 Schedule of reactogenicity assessments

Day	Time	Performed by
0[a]	Baseline: before study product administration	HVTN CRS staff
	Early: 25-60 minutes after all infusions	HVTN CRS staff
	Between early assessment and 11:59pm day 0	HVTN CRS staff or participant
1	Between 12:00am and 11:59pm day 1	HVTN CRS staff or participant
2	Between 12:00am and 11:59pm day 2	HVTN CRS staff or participant
3[b]	Between 12:00am and 11:59pm day 3	HVTN CRS staff or participant

[a] Day of study product administration

[b] New or unresolved reactogenicity symptoms present on day 3 are followed until resolution

9.10.1 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.

Body temperature is measured by oral or infrared thermometry and reported in degrees Celsius. If temperature is measured in Fahrenheit, the conversion to Celsius should be documented in the participant's chart note. A measurement is taken once daily during the assessment period and should be repeated if participant is feeling feverish.

9.10.2 Assessment of infusion site

Infusion site reactions may include redness or erythema and induration or swelling. 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.

9.11 Visit windows and missed visits

Visit windows are defined in HVTN 116 Study Specific Procedures. 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, HVTN

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 7.3.2 and Section 7.3.3 for resolution.

9.12 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, and chemistry panel), pregnancy testing, social impact assessment, biopsy acceptability questionnaire, and HIV test. For participants who have a confirmed diagnosis of HIV infection, see Section 9.14.

9.13 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given and no more mucosal biopsies will be collected during the pregnancy, but remaining visits and other study procedures should be completed unless medically contraindicated. For participants who are no longer pregnant, see Section 7.3.1. 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.

9.14 HIV infection during the study

If a participant becomes HIV-infected during the course of the study, no additional study product will be administered. Participants will be encouraged to continue scheduled study visits for up to 16 weeks following their last study product administration. Follow-up duration for participants diagnosed with HIV infection may be adjusted in consultation with the CRS investigator and the HVTN 116 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At post-infection follow-up visits, only specimens required for protocol-specified safety laboratory tests will be collected; in addition, some clinic procedures may be modified or discontinued (see Appendix H, Appendix I, Appendix J, Appendix K, Appendix L, Appendix M, Appendix N, and Appendix O).

10 Laboratory

10.1 HVTN CRS laboratory procedures

The HVTN 116 Site Lab Instructions provide further guidelines for operational issues concerning the clinical and processing laboratories. This document includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix H, Appendix I, Appendix J, and Appendix K. 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.

10.2 Total blood volume

Required blood volumes per visit are shown in Appendix H, Appendix I, Appendix J, and Appendix K. 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, in which case, 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 (includes estimated maximal blood loss associated with the biopsy procedures).

10.3 Drug detection and quantitation

10.3.1 VRC01/VRC01LS mAb levels in serum, mucosal tissue lysates and mucosal secretions

VRC01/VRC01LS levels will be measured in serum, semen, cervicovaginal secretions, rectal secretions, and mucosal tissue lysates prepared from cervical, vaginal and rectal biopsies collected at the designated timepoints. A quantitative assay (such as an ELISA), binding multiplex antibody assay (BAMA), or Singulex assay may be used to determine the concentration of VRC01/VRC01LS in the aforementioned samples and/or to assess their binding to various Env proteins, such as Consensus gp120, Consensus gp140 and CD4 binding site proteins. ELISA assays employing two different antigens may be used for VRC01/VRC01LS quantitation. One assay employs the resurfaced core 3 antigen (RSC3), designed for selective detection of CD4 binding site bNAbs, such as VRC01/VRC01LS (46). The other assay 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 operational sensitivity of the BAMA and ELISAs with respect to the various sample specimens will be determined for the clinical grade VRC01/VRC01LS mAbs used for this study. However, ongoing studies currently indicate that the interim lower LOD for VRC01 mAb is ≤ 129 +/- 30 ng/ml, 125 +/- 22 ng/ml, and 93 +/- 14 ng/ml in serum, semen, and saliva, respectively, using RSC3 protein on the BAMA platform (with validated plasma LOD of 2.3 -8.0 ng/ml). The LOQ of the validated ELISA using the VRC01 Fab-specific 5C9 mAb is currently 1.1 mcg/mL in serum. The Singulex assay combines a proprietary digital Single Molecule Counting (SMC) technology with a robust microparticle-based immunoassay utilizing the mAb 5C9 to provide higher sensitivity (lower limit of quantification = 50 pg/mL) and broad dynamic range. As the technology for all of these assays continues to develop, an updated assay(s) may be utilized. Any assay that may be used for this study will first be qualified, at a minimum, for linearity, precision, and accuracy.

10.3.2 Immunohistochemistry

The presence of VRC01/VRC01LS and its distribution in cervical, vaginal and rectal tissue will be assessed using immunohistochemical (IHC) methods employing biotinylated versions of mAb 5C9 or RSC3, on optimum cutting temperature (OCT) medium or paraffin embedded biopsies collected at the designated timepoints. The distribution of VRC01/VRC01LS will be described qualitatively or semi-quantitatively relative to the mucosal epithelium, stroma and/or lamina propria. The assay has been used to assess the distribution VRC01/VRC01LS in mucosal tissues from NHP infused with these mAbs and is being adapted for use with human mucosal tissues. As the technology for this assay continues to develop, updated versions may be utilized.

To assess the immunological and inflammatory milieu within which the infused mAbs are found (or not) in the cervical, vaginal and/or rectal compartments, additional IHC assays may be utilized. These assays may include the detection of various Fc receptors, including FcRn, effector cell/inflammatory cell infiltrates and other markers of local inflammation.

10.4 Drug functionality

10.4.1 Infectivity assay

Cervical, vaginal and rectal biopsies will be used to assess the protection provided by VRC01 and VRC01LS at different timepoints post infection. The assay uses immediate challenge of the biopsy tissue *ex vivo*. Currently, the assay measures luminescence from nanoluciferase as a readout of viral replication kinetics in the tissue explant.

We may use several challenge viruses with differential susceptibility to VRC01 neutralization, and may conduct the infection assay in the presence of the participant's serum to explore if serum antibody levels can be protective.

10.4.2 Anti-VRC01/VRC01LS antibody assay

Assessment for development of anti-VRC01/VRC01LS antibodies in subjects will be performed using the Meso Scale Discovery (MSD) platform based on electrochemiluminescence. Serial dilutions of sera/plasma samples are incubated with optimized concentrations of biotinylated VRC01 and SULFO-TAG labeled VRC01 at 2-8°C overnight. Samples are transferred to a Biotin-coated MSD plate and incubated for 1 hour at room temperature. Samples are read with the MSD-2400 with end point dilutions defined as the greatest sample dilution with a response above the positivity threshold for the assay. This assay is independent of the anti-VRC01 antibody isotype, and permits the detection of both high and low affinity antibodies.

The same assay format will be utilized for anti-VRC01LS, with reagents specific for that protein.

10.4.3 Neutralizing antibody assay

Depending upon the concentrations measured in collected specimens, the functional capacity of infused VRC01/VRC01LS (in serum and mucosal secretions) to neutralize HIV may be evaluated by an *in vitro* cell-based virus neutralization assay (65-67) using pseudotyped viruses.

One or more viruses, including those matching the Envs encoded by *ex vivo* challenge viruses that range from highly to moderately sensitive to VRC01 (eg, MN.3, BaL26 and DU151.2), will be assayed. The IC_{50} of VRC01 against MN.3, BaL26 and DU151.2 are in the range of 0.04 mcg/mL (MN.3 and BaL26) and ~4.0 mcg/mL (DU151.2). The IC_{80} values of VRC01 against these viruses are around 0.07, 0.15 and 45.3 mcg/mL, respectively. The TZM-bl assay is validated for this range of sensitivities. It has been shown that the neutralization potency and breadth are similar between VRC01 and VRC01LS (49).

10.5 Genotyping

Fc-receptor, CCR5 delta-32 and human leukocyte antigen (HLA) molecular genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline. Other markers, such as genes associated with immune functions or HIV-1 disease progression, may also be assessed.

10.6 Exploratory studies

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

10.7 Other use of stored specimens

The HVTN stores 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, 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 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.

10.8 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, collecting of tissue, 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.

11 Safety monitoring and safety review

11.1 Safety monitoring and oversight

11.1.1 HVTN 116 PSRT

The HVTN 116 PSRT is composed of the following members:

- DAIDS medical officer representative,
- Protocol chair and cochair,
- Protocol Team leader,
- Core medical monitor,
- Clinical safety specialist, and
- Regional Medical Liaison (RML).

The clinician members of HVTN 116 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, project manager, product developer representative, clinical trial manager, and others may also be included in HVTN 116 PSRT meetings.

11.1.2 HVTN SMB

The SMB is a multidisciplinary group consisting of biostatisticians, clinicians, and experts in HIV prevention research that, collectively, has experience in the conduct and monitoring of HIV prevention trials. Members of the SMB are not directly affiliated with the protocols under review.

The SMB reviews safety data, unblinded as to treatment arm, approximately every 4 months. The reviews consist of evaluation of cumulative reactogenicity events, AE, laboratory safety data, and individual reports of adverse events requiring expedited reporting to DAIDS. To increase the sensitivity for detecting potential safety problems, the SMB will review safety data aggregated across multiple protocols that use the same or similar prevention approaches. The SMB conducts additional special reviews at the request of the HVTN 116 PSRT.

Study sites will receive SMB summary minutes and are responsible for forwarding them to their IRB/EC and any applicable RE.

11.1.3 SDMC 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 HVTN clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 116 PSRT and HVTN SMB (Section 11.1.2);

11.1.4 HVTN Core roles and responsibilities in safety monitoring

The roles and responsibilities of HVTN Core in relation to safety monitoring include:

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 116 PSRT AE review criteria (Section 11.3);
- Notifying HVTN CRSs and other groups when safety pauses are instituted and lifted (Section 11.3);
- Querying HVTN CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 116 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

Sites must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, and 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.

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant 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). All AEs are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected

Version 2.1, July 2017, available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables, except:

- Unintentional weight loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 116 Study Specific Procedures);

- Infusion Site Erythema or Redness and Infusion Site Induration or Swelling will not consider interference with usual social and functional activities such that:
  - Grade 1 is: 2.5 to < 5 cm in diameter OR 6.25 to < 25 cm^2 surface area;
  - Grade 2 is: ≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm^2 surface area;
  - Grade 3 is: ≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage;
  - Grade 4 is: Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue);

- Infusion reactions

All 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 11.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 11.3).

Sites are expected to notify the CSS or RML of any serious safety concern requiring their attention (Table 11-1). Telephone numbers and email addresses are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn116). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, the CSS or RML will reply during working hours (ie, US Pacific Time, South African Standard Time) to confirm that the email has been received and reviewed. If email service is not available, the HVTN 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.

11.2.3 Expedited reporting of adverse events to DAIDS

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

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting. For questions about DAERS, please contact NIAID CRMS Support at CRMSsupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited AE reporting, please contact the DAIDS RSC Safety Office at (DAIDSRSCSafetyOffice@tech-res.com).

The study products for which expedited reporting is required are:

- VRC01 (VRC-HIVMAB060-00-AB)
- VRC01LS (VRC_HIVMAB080-00-AB)

While the participant is in the study reporting period (from the first study product administration until the last scheduled clinic visit), the SAE Reporting Category will be used.

After the protocol-defined AE reporting period for the study, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions as defined in Version 2.0 of the DAIDS EAE Manual must be reported to DAIDS, if the study staff become aware of the events.

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).

11.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all infusions 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 116 PSRT AE review are summarized in Table 11-1. 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 116 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the infusion schedule are listed in Section 7.3.

Table 11-1 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	HVTN CRS action[a]	HVTN Core action
SAE, related	Grade 5 or Grade 4	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 116 PSRT notification
SAE, related	Grade 3	Email and submit forms immediately	Prompt HVTN 116 PSRT AE review to consider pause
AE[b], related	Grade 4 or 3	Email and submit forms immediately	Prompt HVTN 116 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/hvtn116).

[b] Does not include subjective reactogenicity symptoms (infusion site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, and nausea). Does include pruritus, which should be reviewed promptly.

For all safety pauses, HVTN Core notifies the HVTN 116 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the SMB.

Once a trial is paused, the HVTN 116 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of infusions is appropriate, consulting the SMB if necessary. HVTN Core notifies the participating HVTN 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 116 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 116 PSRT notification or prompt HVTN 116 PSRT AE review is triggered, HVTN Core notifies the HVTN 116 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 116 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN requires that each CRS submit to its IRB/EC and any applicable RE protocol-related safety information (such as IND safety reports, notification of infusion 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 116 PSRT (Section 11.4.2).

11.4 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 HVTN CRSs. Events are tracked by internal reports until resolution.

11.4.1 Daily review

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 116 PSRT AE review criteria.

11.4.2 Weekly review

During the infusion phase of the trial, the HVTN 116 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. After the infusions and the following two-week safety visit are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 116 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the HVTN CRS clinic coordinator for verification.

11.5 Study termination

This study may be terminated early by the determination of the HVTN 116 PSRT, HVTN SMB, FDA, SAHPRA, NIH, Office for Human Research Protections (OHRP), or product developer. In addition, the conduct of this study at an individual HVTN CRS may be terminated by the determination of the IRB/EC and any applicable RE.

12 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with the principles of GCP (ICHe6), and according to DAIDS and HVTN policies and procedures as specified in the *HVTN Manual of Operations,* 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;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the clinical trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Ancillary studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS and HVTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 116 *Study Specific Procedures.*

12.1 Social impacts

Participants in this study risk experiencing discrimination or other personal problems, resulting from the study participation itself. The HVTN CRS is obliged to provide advocacy for and assistance to participants regarding these negative social impacts associated with the clinical trial. If HVTN CRS staff have questions regarding ways to assist a participant dealing with a social impact, a designated NIAID or HVTN Core representative can be contacted.

Social harms are tabulated by the SDMC and are subjected to descriptive analysis. The goal is to reduce their incidence and enhance the ability of study staff to mitigate them when possible.

Summary tables of social impact events will be generated weekly, and made available for review by the protocol chairs, protocol team leader, and the designated NIAID representative.

12.2 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.

13 Version history

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

The version history of, and modifications to, Protocol HVTN 116 are described below.

Protocol history and modifications

Date: August 3, 2018

Protocol version: Version 2.0
Protocol modification: Full Protocol Amendment 1

Item 1 Added in Appendices A, B, and E: Broad regulatory agency access to participant study records

Item 2 Updated in Section 11.5, Section 15, and Appendices A, B, E: MCC changed to SAHPRA

Item 3 Added in Section 8.4, Administration, in-line filter language

Item 4 Clarified in Section 9.3: conditions upon when a participant may be replaced after enrollment

Item 5 Clarified in Section 9.6 and Appendices H and I: vaginal biopsies can still be collected at late visits if the total number of biopsies has not been reached

Item 6 Updated based on revisions made in Letter of Amendment 2 to Version 1.0 (US sites), dated September 18, 2017 and Amendment to Version 1.1 (RSA site), dated October 5, 2017

Item 7 Updated based on revisions made in Letter of Amendment 1 (US sites) and Clarification Memo 3 (RSA site) to Version 1.0, dated March 24, 2017

Item 8 Updated based on revisions made in Clarification Memo 2 to Version 1.0, dated December 16, 2016

Item 9 Updated based on revisions made in Clarification Memo 1 to Version 1.0, dated June 17, 2016

Item 10 Per live template changes on May 22, 2018, HIV infection moved from Section 7.3.6, Participant termination from the study, to Section 7.3.3, Discontinuing study product administrations for a participant, and other sections updated

Date: September 18, 2017

Protocol version: Version 1.0
Protocol modification: Letter of Amendment 2 / Same changes made in Version 1.1, dated October 5, 2017 for South African sites

Item 1 Revised in Section 3, *Overview*; Section 5, *Objectives and endpoints*; Section 6, *Statistical considerations*; Appendices A and B, *Sample informed consent forms*: enrollment/sample sizes in Groups 3 and 5

Item 2 References to the DAIDS table for grading of adverse events updated to current version 2.1 and clarifications to the protocol to be consistent with new version of the grading table

Item 3 Clarified in Appendices L and M, *Procedures at HVTN CRS*: duration of screening period in footnote "a"

Item 4 Updated in Section 8*, Study product preparation and administration*: revisions regarding VRC01 and VRC01LS based on the updated IBs

Date: March 24, 2017

Protocol version: Version 1.0
Protocol modification: Letter of Amendment 1 / Clarification Memo 3 (same content)

Item 1 Clarified in Section 6.3, *Blinding*: lab staff will likely not be blinded to group assignment

Item 2 Clarified in Section 7.3.1 *Delaying infusions for a participant*, Section 7.3.3 *Discontinuing study product administrations for a participant, and* Section 7.3.4 *Delaying biopsy collections for a participant*: details regarding participation in the study in the event of a pregnancy

Item 3 Updated in Section 8.2, *Study product formulation*: VRC01 and VRC01LS descriptions

Item 4 Revised in Section 8.3, *Preparation of study products*: IV infusion preparation instructions and holding times for study products after preparation

Item 5 Added the requirement for an in-line filter to be in place for all IV administrations in Section 8.4, *Administration*

Item 6 Updated in Section 8.4, *Administration*: Minimum infusion time period

Item 7 Clarified in Section 10.3.2, *Immunohistochemistry*: biopsy collection instructions

Item 8 Clarified in Section 11.3, *Safety pause and prompt PSRT AE review*, Table 11-1: pruritus is a subjective reactogenicity symptom

Item 9 Clarified in Appendix M, *Procedures at HVTN CRS for Group 3*, Visit 19 Colorectal biopsy collection

Date: December 16, 2016

Protocol version: Version 1.0
Protocol modification: Clarification Memo 2

Item 1 Clarification in Section 9.3, *Enrollment visits*, Section 9.5, *Follow-up visits*, Appendices H-K, *Laboratory procedures*, and Appendices L-O,

Procedures at HVTN CRS: blood hormone levels will be assessed in persons born female only

Date: June 17, 2016

Protocol version: Version 1.0
Protocol modification: Clarification Memo 1

Item 1 Deleted in Section 7.3.3, *Discontinuing study product administrations for a participant*: incorrect instruction for discontinuing infusions

Item 2 Clarified Section 9.6, *Mucosal sampling*: procedures for cervicovaginal secretion collections and pregnancy testing

Item 3 Corrected blood draw volumes in Appendices J & K: Laboratory procedures for Groups 4 and 5

Date: April 22, 2016

Protocol version: 1.0
Protocol modification: Original protocol

14 Document references (other than literature citations)

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

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf.
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
- Division of AIDS Protocol Registration Manual. Available at https://www.niaid.nih.gov/sites/default/files/prmanual.pdf
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, July 2017. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 116 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 116 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
- Lab assay algorithm

- HVTN algorithm for diagnosis of HIV infections. Part of the HVTN Laboratory Manual of Operations (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

- Participants' Bill of Rights and Responsibilities. Accessible through the HVTN website.

- NIH *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. Available athttp://osp.od.nih.gov/biotechnology/biosafety/nih-guidelines.

- NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at http://grants1.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html.

- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.

- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at https://www.niaid.nih.gov/sites/default/files/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 16 for literature cited in the background and statistics sections of this protocol.

15 Acronyms and abbreviations

Ab	antibody
Ad	adenovirus
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
β-HCG	beta human chorionic gonadotropin
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
CI	confidence interval
CRF	case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS*	clinical research site
CTL	cytotoxic T lymphocyte
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCV	hepatitis C virus
HLA	human leukocyte antigen
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
IBC	Institutional Biosafety Committee
ICH	International Conference on Harmonisation
IND	Investigational New Drug

IRB	Institutional Review Board
IUD	intrauterine device
MAR	missing at random
MMR	measles, mumps, and rubella
mAb	monoclonal 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
NOEL	no observed effect level
OHRP	US Office for Human Research Protections
OPV	oral polio vaccine
PAB	DAIDS Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PI	Principal Investigator
PK	pharmacokinetics
PSRT	Protocol Safety Review Team
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
SAE	serious adverse event
SAHPRA	South African Health Products Regulatory Authority
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SMB	Safety Monitoring Board
SPT	DAIDS Safety and Pharmacovigilance Team
UW-VSL	University of Washington Virology Specialty Laboratory
VRC	Vaccine Research Center (NIAID)
WT	wild type

* 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.

16 Literature cited

1. UNAIDS. Ethical considerations in biomedical HIV prevention trials. 2007 7/2007. Report No.

2. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. 1979 4/18/1979. Report No.

3. Council for International Organizations of Medical Sciences (CIOMS). International ethical guidelines for biomedical research involving human subjects. Bull Med Ethics. 2002(182):17-23.

4. UNAIDS WipwUa. Global Report on HIV Treatment 2013: Results, Impact and Opportunities. 2014 6/2014. Report No.

5. UNAIDS. Local Epidemics Issues Brief. 2014 2014. Report No.

6. UNAIDS. The GAP Report. 2014 2014. Report No.

7. Vittinghoff E, Douglas J, Judson F, McKirnan D, MacQueen K, Buchbinder SP. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. Am J Epidemiol. 1999;150(3):306-11.

8. Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis. 2009;9(2):118-29.

9. Jin F, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JC, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS. 2010;24(6):907-13.

10. Winokur PL, Stapleton JT. Immunoglobulin prophylaxis for hepatitis A. Clin Infect Dis. 1992;14(2):580-6.

11. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2006;55(RR-7):1-23.

12. Graham BS, Ambrosino DM. History of passive antibody administration for prevention and treatment of infectious diseases. Curr Opin HIV AIDS. 2015;10(3):129-34.

13. Palivizumab, a Humanized Respiratory Syncytial Virus Monoclonal Antibody, Reduces Hospitalization From Respiratory Syncytial Virus Infection in High-risk Infants. Pediatrics. 1998;102(3):531-7.

14. Carbonell-Estrany X, Simoes EA, Dagan R, Hall CB, Harris B, Hultquist M, et al. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a noninferiority trial. Pediatrics. 2010;125(1):e35-e51.

15. Homaira N, Rawlinson W, Snelling TL, Jaffe A. Effectiveness of Palivizumab in Preventing RSV Hospitalization in High Risk Children: A Real-World Perspective. Int J Pediatr. 2014;2014:571609.

16. Li Y, Migueles SA, Welcher B, Svehla K, Phogat A, Louder MK, et al. Broad HIV-1 neutralization mediated by CD4-binding site antibodies. Nat Med. 2007;13(9):1032-4.

17. Simek MD, Rida W, Priddy FH, Pung P, Carrow E, Laufer DS, et al. Human immunodeficiency virus type 1 elite neutralizers: individuals with broad and potent neutralizing activity identified by using a high-throughput neutralization assay together with an analytical selection algorithm. J Virol. 2009;83(14):7337-48.

18. Wu X, Yang ZY, Li Y, Hogerkorp CM, Schief WR, Seaman MS, et al. Rational design of envelope identifies broadly neutralizing human monoclonal antibodies to HIV-1. Science. 2010;329(5993):856-61.

19. Zhou T, Georgiev I, Wu X, Yang ZY, Dai K, Finzi A, et al. Structural basis for broad and potent neutralization of HIV-1 by antibody VRC01. Science. 2010;329(5993):811-7.

20. Gray ES, Taylor N, Wycuff D, Moore PL, Tomaras GD, Wibmer CK, et al. Antibody specificities associated with neutralization breadth in plasma from human immunodeficiency virus type 1 subtype C-infected blood donors. J Virol. 2009;83(17):8925-37.

21. Gray ES, Madiga MC, Hermanus T, Moore PL, Wibmer CK, Tumba NL, et al. The neutralization breadth of HIV-1 develops incrementally over four years and is associated with CD4+ T cell decline and high viral load during acute infection. J Virol. 2011;85(10):4828-40.

22. Corti D, Langedijk JP, Hinz A, Seaman MS, Vanzetta F, Fernandez-Rodriguez BM, et al. Analysis of memory B cell responses and isolation of novel monoclonal antibodies with neutralizing breadth from HIV-1-infected individuals. PLoS ONE. 2010;5(1):e8805.

23. Walker LM, Huber M, Doores KJ, Falkowska E, Pejchal R, Julien JP, et al. Broad neutralization coverage of HIV by multiple highly potent antibodies. Nature. 2011;477(7365):466-70.

24. Scheid JF, Mouquet H, Ueberheide B, Diskin R, Klein F, Oliveira TY, et al. Sequence and structural convergence of broad and potent HIV antibodies that mimic CD4 binding. Science. 2011;333(6049):1633-7.

25. Binley JM, Lybarger EA, Crooks ET, Seaman MS, Gray E, Davis KL, et al. Profiling the specificity of neutralizing antibodies in a large panel of plasmas from patients chronically infected with human immunodeficiency virus type 1 subtypes B and C. J Virol. 2008;82(23):11651-68.

26. Sather DN, Armann J, Ching LK, Mavrantoni A, Sellhorn G, Caldwell Z, et al. Factors associated with the development of cross-reactive neutralizing antibodies during human immunodeficiency virus type 1 infection. J Virol. 2009;83(2):757-69.

27. Falkowska E, Ramos A, Feng Y, Zhou T, Moquin S, Walker LM, et al. PGV04, an HIV-1 gp120 CD4 binding site antibody, is broad and potent in neutralization but does not induce conformational changes characteristic of CD4. J Virol. 2012;86(8):4394-403.

28. Walker LM, Phogat SK, Chan-Hui PY, Wagner D, Phung P, Goss JL, et al. Broad and potent neutralizing antibodies from an African donor reveal a new HIV-1 vaccine target. Science. 2009;326(5950):285-9.

29. Walker LM, Simek MD, Priddy F, Gach JS, Wagner D, Zwick MB, et al. A limited number of antibody specificities mediate broad and potent serum neutralization in selected HIV-1 infected individuals. PLoS Pathog. 2010;6(8):e1001028.

30. Stamatatos L, Morris L, Burton DR, Mascola JR. Neutralizing antibodies generated during natural HIV-1 infection: good news for an HIV-1 vaccine? Nat Med. 2009;15(8):866-70.

31. Walker LM, Burton DR. Rational antibody-based HIV-1 vaccine design: current approaches and future directions. Curr Opin Immunol. 2010;22(3):358-66.

32. Burton DR, Ahmed R, Barouch DH, Butera ST, Crotty S, Godzik A, et al. A Blueprint for HIV Vaccine Discovery. Cell Host Microbe. 2012;12(4):396-407.

33. Burton DR, Stanfield RL, Wilson IA. Antibody vs. HIV in a clash of evolutionary titans. Proc Natl Acad Sci U S A. 2005;102(42):14943-8.

34. Kwong PD, Mascola JR. Human antibodies that neutralize HIV-1: identification, structures, and B cell ontogenies. Immunity. 2012;37(3):412-25.

35. Georgiev IS, Gordon JM, Zhou T, Kwong PD. Elicitation of HIV-1-neutralizing antibodies against the CD4-binding site. Curr Opin HIV AIDS. 2013;8(5):382-92.

36. Wu X, Wang C, O'Dell S, Li Y, Keele BF, Yang Z, et al. Selection pressure on HIV-1 envelope by broadly neutralizing antibodies to the conserved CD4-binding site. J Virol. 2012;86(10):5844-56.

37. Lynch RM, Tran L, Louder MK, Schmidt SD, Cohen M, Dersimonian R, et al. The Development of CD4 Binding Site Antibodies During HIV-1 Infection. J Virol. 2012;86(14):7588-95.

38. Pyzik M, Rath T, Lencer WI, Baker K, Blumberg RS. FcRn: The Architect Behind the Immune and Nonimmune Functions of IgG and Albumin. J Immunol. 2015;194(10):4595-603.

39. Roopenian DC, Christianson GJ, Sproule TJ, Brown AC, Akilesh S, Jung N, et al. The MHC class I-like IgG receptor controls perinatal IgG transport, IgG homeostasis, and fate of IgG-Fc-coupled drugs. J Immunol. 2003;170(7):3528-33.

40. Wani MA, Haynes LD, Kim J, Bronson CL, Chaudhury C, Mohanty S, et al. Familial hypercatabolic hypoproteinemia caused by deficiency of the neonatal Fc receptor, FcRn, due to a mutant beta2-microglobulin gene. Proc Natl Acad Sci U S A. 2006;103(13):5084-9.

41. Akilesh S, Christianson GJ, Roopenian DC, Shaw AS. Neonatal FcR expression in bone marrow-derived cells functions to protect serum IgG from catabolism. J Immunol. 2007;179(7):4580-8.

42. Gupta S, Pegu P, Venzon DJ, Gach JS, Ma ZM, Landucci G, et al. Enhanced in vitro transcytosis of simian immunodeficiency virus mediated by vaccine-induced antibody predicts transmitted/founder strain number after rectal challenge. J Infect Dis. 2015;211(1):45-52.

43. Yoshida M, Kobayashi K, Kuo TT, Bry L, Glickman JN, Claypool SM, et al. Neonatal Fc receptor for IgG regulates mucosal immune responses to luminal bacteria. J Clin Invest. 2006;116(8):2142-51.

44. Tzaban S, Massol RH, Yen E, Hamman W, Frank SR, Lapierre LA, et al. The recycling and transcytotic pathways for IgG transport by FcRn are distinct and display an inherent polarity. J Cell Biol. 2009;185(4):673-84.

45. Pudney J, Anderson DJ. Immunobiology of the human penile urethra. Am J Pathol. 1995;147(1):155-65.

46. Gupta S, Gach JS, Becerra JC, Phan TB, Pudney J, Moldoveanu Z, et al. The Neonatal Fc receptor (FcRn) enhances human immunodeficiency virus type 1 (HIV-1) transcytosis across epithelial cells. PLoS Pathog. 2013;9(11):e1003776.

47. Li Z, Palaniyandi S, Zeng R, Tuo W, Roopenian DC, Zhu X. Transfer of IgG in the female genital tract by MHC class I-related neonatal Fc receptor (FcRn) confers protective immunity to vaginal infection. Proc Natl Acad Sci U S A. 2011;108(11):4388-93.

48. Armitage CW, O'Meara CP, Harvie MC, Timms P, Blumberg RS, Beagley KW. Divergent outcomes following transcytosis of IgG targeting intracellular and extracellular chlamydial antigens. Immunol Cell Biol. 2014;92(5):417-26.

49. Ko SY, Pegu A, Rudicell RS, Yang ZY, Joyce MG, Chen X, et al. Enhanced neonatal Fc receptor function improves protection against primate SHIV infection. Nature. 2014;514(7524):642-5.

50. Shingai M, Donau OK, Plishka RJ, Buckler-White A, Mascola JR, Nabel GJ, et al. Passive transfer of modest titers of potent and broadly neutralizing anti-HIV monoclonal antibodies block SHIV infection in macaques. J Exp Med. 2014;211(10):2061-74.

51. Pegu A, Yang ZY, Boyington JC, Wu L, Ko SY, Schmidt SD, et al. Neutralizing antibodies to HIV-1 envelope protect more effectively in vivo than those to the CD4 receptor. Sci Transl Med. 2014;6(243):243ra88.

52. Moldt B, Rakasz EG, Schultz N, Chan-Hui PY, Swiderek K, Weisgrau KL, et al. Highly potent HIV-specific antibody neutralization in vitro translates into effective protection against mucosal SHIV challenge in vivo. Proc Natl Acad Sci U S A. 2012;109(46):18921-5.

53. Zalevsky J, Chamberlain AK, Horton HM, Karki S, Leung IW, Sproule TJ, et al. Enhanced antibody half-life improves in vivo activity. Nat Biotechnol. 2010;28(2):157-9.

54. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, et al. Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. Regul Toxicol Pharmacol. 2009;54(2):164-82.

55. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004;93(11):2645-68.

56. Lynch RM, Boritz E, Coates EE, DeZure A, Madden P, Costner P, et al. Virologic effects of broadly neutralizing antibody VRC01 administration during chronic HIV-1 infection. Sci Transl Med. 2015;7(319):319ra206.

57. Ledgerwood JE, Coates EE, Yamshchikov G, Saunders JG, Holman L, Enama ME, et al. Safety, pharmacokinetics and neutralization of the broadly neutralizing HIV-1 human monoclonal antibody VRC01 in healthy adults. Clin Exp Immunol. 2015;182(3):289-301.

58. Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ. The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov. 2010;9(4):325-38.

59. Bugelski PJ, Achuthanandam R, Capocasale RJ, Treacy G, Bouman-Thio E. Monoclonal antibody-induced cytokine-release syndrome. Expert Rev Clin Immunol. 2009;5(5):499-521.

60. Vogel WH. Infusion reactions: diagnosis, assessment, and management. Clin J Oncol Nurs. 2010;14(2):E10-E21.

61. Hasselrot K, Cheruiyot J, Kimani J, Ball TB, Kaul R, Hirbod T. Feasibility and safety of cervical biopsy sampling for mucosal immune studies in female sex workers from Nairobi, Kenya. PLoS ONE. 2012;7(10):e47570.

62. McGowan I, Hoesley C, Cranston RD, Andrew P, Janocko L, Dai JY, et al. A phase 1 randomized, double blind, placebo controlled rectal safety and acceptability study of tenofovir 1% gel (MTN-007). PLoS ONE. 2013;8(4):e60147.

63. Thurman A. Safety of Cervical and Vaginal Biopsies in Microbicide and Contraceptive Research. 2015.

64. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat. 1998;52(2):119-26.

65. Montefiori DC. Measuring HIV neutralization in a luciferase reporter gene assay. Methods Mol Biol. 2009;485:395-405.

66. Todd CA, Greene KM, Yu X, Ozaki DA, Gao H, Huang Y, et al. Development and implementation of an international proficiency testing program for a neutralizing antibody assay for HIV-1 in TZM-bl cells. J Immunol Methods. 2012;375(1-2):57-67.

67. Ozaki DA, Gao H, Todd CA, Greene KM, Montefiori DC, Sarzotti-Kelsoe M. International technology transfer of a GCLP-compliant HIV-1 neutralizing antibody assay for human clinical trials. PLoS ONE. 2012;7(1):e30963.

Appendix A Sample informed consent form for Groups 1-3

Title: A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

HVTN protocol number: HVTN 116

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) and [Insert site name] are doing a study to test 2 versions of an antibody against HIV called VRC01 and VRC01LS. HIV is the virus that causes AIDS. Antibodies are one of the ways the human body fights infection. Antibodies are natural proteins that the body can make to prevent infectious agents such as bacteria and viruses from making you sick. 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.

Originally, about 101 people were planned to take part in this study at multiple sites. The study has since been changed so that now only about 74 people will take part in it. The two groups (Groups 3 and 5) that are testing the VRC01LS antibody will stop enrolling because the researchers feel that a smaller number of participants is enough to provide the information needed regarding the VRC01LS antibody. Enrollment will stop once at least 12 people have enrolled in Group 3 and Group 5 combined. Participants that have enrolled in these two groups will continue their study schedule as planned, and should complete all study visits, as the information collected will be important for the research. 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.**

   - Are the antibodies safe to give to people?

- Are people able to take the antibodies without becoming too uncomfortable?
- Do the antibodies move around in the body?
- Do the antibodies get to where they need to be in the body to protect people from HIV?
- How much of the antibodies remain in your body as time passes?

2. The antibodies cannot give you HIV.

The antibodies are not made from actual HIV. It is impossible for the antibodies to give you HIV. Also, they 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. These antibodies are experimental.

The 2 versions of the antibody are called VRC-HIVMAB060-00-AB and VRC-HIVMAB080-00-AB. They are both antibodies against the HIV virus. From here on, we will call them VRC01 and VRC01LS or the antibodies.

They are experimental. That means we do not know whether they will be safe to use in people, or whether they will work to prevent HIV infection. These antibodies are used only in research studies.

The antibodies were developed by the Vaccine Research Center at the US National Institutes of Health (NIH). In laboratory and animal studies, the antibodies attached to and disabled many kinds of HIV viruses. We do not know if they will act the same way when given to people. It will take many studies to learn if they will be useful for prevention of HIV or treatment of HIV. This study alone will not answer these questions.

VRC01 and VRC01LS are identical to each other except for a small structural change in VRC01LS. The purpose of this change is to make VRC01LS last longer in the body.

Risks of the antibodies:

There have been 6 studies using the VRC01 antibody in people in the United States at the NIH Clinical Center and at HVTN clinics. As of February 22, 2018, VRC01 has been given to over 2600 HIV-uninfected and about 88 HIV-infected adults and about 40 HIV-exposed infants. The VRC01 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. The placebo is made from inactive ingredients made to look like the antibody. 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.

There is 1 ongoing study using the VRC01LS antibody for the first time in people in the US at the NIH Clinical Center. As of July 17, 2017, 39 people received the VRC01LS antibody. So far, it has not made them too uncomfortable or caused serious health problems.

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

General risks of antibodies:

Antibodies that are different from the antibodies in this study have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours or, rarely, over a few days to weeks. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, muscle and joint pains, diarrhea, chest discomfort, high or low blood pressure, racing heartbeat , or chest pain, and itchiness, rash, or hives where you got the infusion.

Rarely, an antibody can cause an allergic reaction. If the reaction occurs, it usually occurs soon after getting an antibody. It can include hives, itchiness, or rash, and swelling in the mouth and face with difficulty in breathing. It can also include racing heartbeat, chest pain, and dizziness. With treatment this reaction usually will go away.

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 or VRC01LS 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 other HIV vaccine or HIV prevention studies now or in the future. You cannot be in this study while you are

in another study where you get a study product. Also during the study, you should not donate blood or tissue.

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

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

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

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

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

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 test you for syphilis, chlamydia, gonorrhea, trichomonas vaginalis, bacterial vaginosis, hepatitis B, and hepatitis C. We will ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV.

If you were born female, we will test you for pregnancy. If you have had your ovaries removed (an oophorectomy), verified by medical records, you are not required to have a pregnancy test. If you were born female and are 21 years or older you may need to have a Pap smear if you have not had one within the last 3-5 years.

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

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

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

   For the care that we cannot give, we will explain how we will help you get care elsewhere. For health problems that are unrelated to the study, we will not pay for care.

7. **If you 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 to join this study.**

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

You should not become pregnant during the study because we do not know how the antibodies could affect the developing baby. You must agree to use effective birth control from 21 days before enrollment through the last scheduled clinic visit. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

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

8. **You will come to the clinic for scheduled visits about 13-14 times over about 1 to 1½ years.**

Site: Insert number of visits and range of visit lengths. (There is site-specific variation in screening protocols and in the number of possible follow-up visits between protocol-mandated visits.)

Visits can last from [#] to [#] hours.

You may have to come for more visits if you have a lab or health issue.

We may contact you after the 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).

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 one of the antibodies by intravenous (IV) infusion.

Everyone will receive one of the antibodies by IV infusion. To get an IV, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small bag of fluid that contains the antibody. An IV pump controls how fast the fluid drips from the bag, through the tube, and into your vein.

11. We will give you the IV infusions on a schedule.

There are 5 groups in this study. You will be in either Group 1, 2 or 3. However, the two groups (Groups 3 and 5) that are testing the VRC01LS antibody may have stopped enrolling so you may only be in either Group 1 or 2. There will be 23 people in Groups 1 and 2. Group 3 will stop enrolling once about 6 people have enrolled. Groups 4 and 5 will not be done at this clinic.

Groups 1 and 2 will get VRC01. Group 1 will get a lower dose than Group 2. 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. Group 3 will get VRC01LS.

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

We have no say in whether you are in Group 1, 2 or 3. It will be random, like flipping a coin. You cannot change groups.

Group	Treatment	IV Infusion Schedule				
		First Infusion	2 months later	3 months later	4 months later	6 months later
Group 1	VRC01 10 mg/kg	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 2	VRC01 30 mg/kg	IV Infusion	IV Infusion		IV Infusion	IV Infusion
Group 3	VRC01LS 30 mg/kg	IV Infusion		IV Infusion		IV Infusion

Each IV infusion will take about 15 to 60 minutes. You will have to wait in the clinic for about a half hour after each infusion to see if there are any problems. Then for that night and for three more days, you will need to keep track of how you are feeling and if you have any symptoms. Contact the clinic staff if you have any issues or concerns after getting an infusion. If you have a problem, we will continue to check on you until it goes away.

12. In addition to giving you one of the antibodies, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you were born female;
- 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;
- Take urine and blood samples.

If you were born female, we will test you at some visits for gonorrhea, chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes simplex virus, and yeast. If you were born male, we will test you at some visits for gonorrhea, herpes simplex virus, and chlamydia.

We will give you your test results. If you need care, we will tell you about the care we can give you here. We will also tell you about care we can help you get elsewhere.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 9 mL and 160 mL (about 2 teaspoons to about 2/3 of a 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 F, 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 review the results of these 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 also collect semen, rectal fluid and tissue, cervical fluid and cervical and vaginal tissue samples from you.

We want to see if the antibodies get to the parts of the body where people may be exposed to HIV: their rectum, vagina, and penis. We will take samples from these areas.

We will ask you to avoid some activities before we collect these samples. This will help make sure your samples give accurate lab readings. There are also some activities we will ask you to avoid after collecting the samples that are described below.

We will ask all participants born male to provide semen as well as rectal fluids and tissue. We will ask all participants born female to provide cervical fluids as well as cervical and vaginal tissues. *For every site except Seattle use this sentence:* If participants born female become uncomfortable providing cervical fluids as well as cervical and vaginal tissues at any time, we will ask you to provide rectal fluids and/or tissues instead.

Seattle site: Insert the following sentences instead.

In addition, we will ask participants born female to provide rectal fluids and tissues. You can decide not to give rectal fluids and tissues and still be in the study.

Site: localize measurement units throughout the following sections as needed.

Semen collections (for persons born male)

You will provide semen at the clinic. We will ask you to ejaculate into a plastic cup, which we will give to you.

For the **2 days before** we collect your semen, we will ask you to follow these instructions:

- Do not ejaculate,
- Do not use anything with lubricants,
- Do not put saliva (your own or someone else's) on the penis,
- Do not receive oral sex.

Rectal fluid collections (for all participants)

We will collect rectal fluid by first placing a plastic tube about 2 cm wide (a little less than an inch) into your rectum. The tube will go in about 6½ cm (about 2½ inches). We will then place in your rectum either a small, absorbent sponge for 5 minutes or an absorbent balloon for less than a minute. The balloon will be inflated to the size of a chicken egg (2 x 1 inches, 5 x 3 cm) after it is inside your rectum, and deflated before it is removed.

For the **2 days before** we collect your rectal fluid, we will ask you to follow these instructions:

- Do not have receptive anal intercourse
- Do not put anything into your anus, including cleaning products (creams, gels, lotions, pads, etc.), lubricant, enemas or douches (even with water)
- Do not use any anti-inflammatory creams in or around your anus.
- We will not collect rectal fluid if you are pregnant, or if we think you may have an anal or rectal infection. You should tell us if your rectal area is sore.

Rectal tissue collections (for all participants)

Cape Town site: include a description of where the biopsies will take place, if needed.

We will collect small samples of tissue about the size of a grain of rice from the lining of your rectum. These are called rectal biopsies. We will collect 5 biopsies at up to 7 different visits. To take the samples, we will place a plastic tube about 2 cm wide (a little less than an inch) into the anus to view the lower part of the rectum. You may feel some discomfort, but the biopsies are almost always painless. It will take about 15 minutes.

You may see blood in your first few stools. This is normal after a biopsy. If you think the bleeding is excessive, contact your study clinician immediately.

For the **2 days before** we collect your rectal tissues, we will ask you to follow the same instructions as above. In addition, we will ask you to follow these instructions after the procedure:

- Do not have rectal sex and/or insert any foreign object or substance into the rectum for **5 days after** biopsy samples have been collected;
- You should call the clinic if you have a lot of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not getting better.

Cervical fluid collections (for persons born female)

You must have had a Pap smear within the last 3 to 5 years with the most recent result being normal. If you have not had a Pap smear within the last 3 years and would like to get one, we will tell you where you can get one.

We will collect cervical fluids by using either a soft sponge inserted into the opening of your cervix, or by using something call a menstrual cup inserted into your vagina. If we use a soft sponge to collect cervical fluids, we will insert a speculum (a device that holds your vagina open) into your vagina and place the sponge in the opening of the cervix. This is similar to getting a pap smear. If we use the menstrual cup, we will explain how to insert it into your vagina. You may insert it before you come to the clinic. You will wear it for up to 6 hours and

remove it at the clinic. You will insert a second menstrual cup at the clinic and wear it for 10-15 minutes. If you are uncomfortable doing any of this on your own, you may come to the clinic and we will help you.

For the **2 days before** we collect your cervical fluid, we will ask you to follow these instructions:

- Do not use any spermicide, lubricants, douche (even with water), or medication in or around your vagina;
- Do not have vaginal intercourse or insert anything into your vagina;
- Using a vaginal ring for contraception is fine and can continue to be used. You will need to remove it for a few hours before the procedure. The clinic staff can explain this to you.

We will not collect cervical fluid if you are menstruating or pregnant, or if we think you may have a cervical or vaginal infection. If you are menstruating, we may ask you to return to collect this sample at another time.

Cervical and vaginal tissue collections (for persons born female)

We will collect small samples of tissue about the size of a grain of rice. We will collect up to 4 cervical and up to 5 vaginal biopsies at up to 6 different visits. We will insert a speculum into your vagina. A speculum is a metal or plastic tool that looks like a bird's beak. It is used to help open your vagina a few inches.

After the speculum is put into your vagina, the cervix and vaginal wall will be cleaned with a clean cotton ball or swab.

Biopsies will be taken with clean forceps. Forceps are a metal or plastic tool to help get the tissue from inside your vagina and cervix. You may feel cramping, pain or discomfort. We will check to make sure that there is no bleeding from where the biopsies are taken. If there is bleeding, we will use a medication to stop it. One type of medication, silver nitrate, has a gray color. You may see gray flecks in your vaginal discharge after the biopsy. This is normal. The procedure will take about 15 minutes.

For the **2 days before** we collect your cervical/vaginal tissue, we will ask you to follow the same instructions as above. In addition, we will ask you to follow these instructions after the procedure:

- Do not have vaginal sex and/or insert any foreign object or substance, including tampons, into the vagina for **7 days after** biopsy samples have been collected;

- Participants should contact the clinic if they experience a large amount of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not improving.

- Using a vaginal ring for contraception is fine and can continue to be used.

14. We will counsel you on avoiding HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your risk of getting HIV low.

15. We will test your samples for this study.

We will send your samples (without your name) to labs approved by the HVTN for this study, which are located in the United States and South Africa. Researchers at these labs will test your samples to see how your immune system responds to the antibodies. In rare cases, some of your samples may be sent to labs approved by the HVTN in other countries for research related to this study.

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

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

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

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

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

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

16. When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies by HVTN 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 part of your medical record. The studies are only being done for research purposes.

Will the HVTN sell my samples and information? No, but the HVTN 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. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN 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, sex, 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, vaccines, antibody mediated prevention, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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

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

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

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

People who may see your information are:

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

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

17. 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 and its study monitors,
- The US Food and Drug Administration,
- South African Health Products Regulatory Authority (SAHPRA),
- [Insert name of local IRB/EC] ,
- Any regulatory agency that reviews clinical trials,
- The HVTN and people who work for them,
- The HVTN 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.

When the study is done, we may share the information from the study with others so they can see it and use it. We will not share any information that will let someone identify you.

18. We may stop your infusions 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 infusions.

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

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

19. We will stop your infusions and most sample collections if you become pregnant during the study. We will continue blood draws to check your health.

We will encourage you to stay in the study if you choose. We will discuss your study options with you.

If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

20. If you get infected with HIV during the study, we will stop your study product administration, take fewer samples, and help you get care and support.

We will encourage you to stay in the study for up to 16 weeks if you choose. We will discuss your study options with you. We will counsel you about your HIV infection and about telling your partner(s). We will tell you where you can get support and medical care, and if there are other studies you may want to join. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

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:

In this study, we will take your blood. This can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of IV infusion 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 a blood clot or infection.

Risks of taking rectal and genital fluids and tissues:

We will ask you to stop some activities before and after we collect these samples. You may find this inconvenient. These sample collections may cause some anxiety, temporary discomfort, and embarrassment. We will try to make you as comfortable as possible.

All biopsies may cause a small amount of bleeding, which usually stops on its own. In rare cases, excess bleeding or infection may occur from a biopsy. If you need care, we will tell you about the care we can give you here. We will also tell you about care we can help you get elsewhere.

Until the areas where the biopsies were taken heal, you are at increased risk for HIV infection if you are exposed. Most people heal within 5 to 7 days, but some may take longer.

Personal problems/discrimination:

Some people who join HVTN 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. We do not expect you to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the antibodies and none of them detected the antibody.

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.

Although it has not been seen so far, getting VRC01 or VRC01LS may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

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 antibodies will increase, decrease, or not change your risk of becoming infected with HIV if exposed. If you get infected with HIV, we do not know how the antibodies might affect your HIV infection or how long it takes to develop AIDS.

We do not know how the antibodies will affect a pregnant participant or a developing baby.

Benefits

22. The study may not benefit you.

We do not know whether getting the antibodies might benefit you in any way. 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 help in the search for a vaccine to prevent HIV. However, if the antibodies later become approved and sold, 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 antibodies 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.

Next paragraph for Cape Town site only:

In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury, following 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 has 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 has limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

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

You may disagree with the decision about whether your injury is study related. If you wish, the HVTN will ask independent experts 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].

South African sites, include the following paragraph:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Acting Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001
Tel: (012) 395 8126
Fax: (012) 395 9201
e-mail: portia.nkambule@health.gov.za

Your permissions and signature

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

27. In Section 16 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 keeps track of your decision about how your samples and information can be used.

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

OR

☐ I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐ I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

28. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.
- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix B Sample informed consent form for Groups 4-5

Title: A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

HVTN protocol number: HVTN 116

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) and [Insert site name] are doing a study to test 2 versions of an antibody against HIV called VRC01 and VRC01LS. HIV is the virus that causes AIDS. Antibodies are one of the ways the human body fights infection. Antibodies are natural proteins that the body can make to prevent infectious agents such as bacteria and viruses from making you sick. 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.

Originally, about 101 people were planned to take part in this study at multiple sites. The study has since been changed so that now only about 74 people will take part in it. The two groups (Groups 3 and 5) that are testing the VRC01LS antibody will stop enrolling because the researchers feel that a smaller number of participants is enough to provide the information needed regarding the VRC01LS antibody. Enrollment will stop once at least 12 people have enrolled in Group 3 and Group 5 combined. Participants that have enrolled in these two groups will continue their study schedule as planned, and should complete all study visits, as the information collected will be important for the research. 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.**

   - Are the antibodies safe to give to people?

- Are people able to take the antibodies without becoming too uncomfortable?
- Do the antibodies move around in the body?
- Do the antibodies get to where they need to be in the body to protect people from HIV?
- How much of the antibodies remain in your body as time passes?

2. The antibodies cannot give you HIV.

The antibodies are not made from actual HIV. It is impossible for the antibodies to give you HIV. Also, they 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. These antibodies are experimental.

The 2 versions of the antibody are called VRC-HIVMAB060-00-AB and VRC-HIVMAB080-00-AB. They are both antibodies against the HIV virus. From here on, we will call them VRC01 and VRC01LS or the antibodies.

They are experimental. That means we do not know whether they will be safe to use in people, or whether they will work to prevent HIV infection. These antibodies are used only in research studies.

The antibodies were developed by the Vaccine Research Center at the US National Institutes of Health (NIH). In laboratory and animal studies, the antibodies attached to and disabled many kinds of HIV viruses. We do not know if they will act the same way when given to people. It will take many studies to learn if they will be useful for prevention of HIV or treatment of HIV. This study alone will not answer these questions.

VRC01 and VRC01LS are identical to each other except for a small structural change in VRC01LS. The purpose of this change is to make VRC01LS last longer in the body.

Risks of the antibodies:

There have been 6 studies using the VRC01 antibody in people in the United States at the NIH Clinical Center and at HVTN clinics. As of February 22, 2018, VRC01 has been given to over 2600 HIV-uninfected and about 88 HIV-infected adults and about 40 HIV-exposed infants. The VRC01 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. The placebo is made from inactive ingredients made to look like the antibody. 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.

There is 1 ongoing study using the VRC01LS antibody for the first time in people in the US at the NIH Clinical Center. As of July 17, 2017, 39 people received the VRC01LS antibody. So far, it has not made them too uncomfortable or caused serious health problems.

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

General risks of antibodies:

Antibodies that are different from the antibodies in this study have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours or, rarely, over a few days to weeks. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, muscle and joint pains, diarrhea, chest discomfort, high or low blood pressure, racing heartbeat , or chest pain, and itchiness, rash, or hives where you got the infusion.

Rarely, an antibody can cause an allergic reaction. If the reaction occurs, it usually occurs soon after getting an antibody. It can include hives, itchiness, or rash, and swelling in the mouth and face with difficulty in breathing. It can also include racing heartbeat, chest pain, and dizziness. With treatment this reaction usually will go away.

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 or VRC01LS 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 other HIV vaccine or HIV prevention studies now or in the future. You cannot be in this study while you are

in another study where you get a study product. Also during the study, you should not donate blood or tissue.

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

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

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

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

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

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 test you for syphilis, chlamydia, gonorrhea, trichomonas vaginalis, bacterial vaginosis, hepatitis B, and hepatitis C. We will ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV.

If you were born female, we will test you for pregnancy. If you have had your ovaries removed (an oophorectomy), verified by medical records, you are not required to have a pregnancy test. If you were born female and are 21 years or older you may need to have a Pap smear if you have not had one within the last 3-5 years.

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

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

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

   For the care that we cannot give, we will explain how we will help you get care elsewhere. For health problems that are unrelated to the study, we will not pay for care.

7. **If you 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 to join this study.**

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

You should not become pregnant during the study because we do not know how the antibodies could affect the developing baby. You must agree to use effective birth control from 21 days before enrollment through the last scheduled clinic visit. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

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

8. **You will come to the clinic for scheduled visits about 7-9 times over about 6 months to 1 year.**

Site: Insert number of visits and range of visit lengths. (There is site-specific variation in screening protocols and in the number of possible follow-up visits between protocol-mandated visits.)

Visits can last from [#] to [#] hours.

You may have to come for more visits if you have a lab or health issue.

We may contact you after the 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).

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 one of the antibodies by intravenous (IV) infusion.

Everyone will receive one of the antibodies by IV infusion. To get an IV, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small bag of fluid that contains the antibody. An IV pump controls how fast the fluid drips from the bag, through the tube, and into your vein. We will give you one IV infusion.

11. We will give you the IV infusions on a schedule.

There are 5 groups in this study. You will be in either Group 4 or 5. However, the two groups (Groups 3 and 5) that are testing the VRC01LS antibody may have stopped enrolling so you may only be Group 4. There will be 16 people in Group 4. Group 5 will stop enrolling once about 6 people have enrolled. Groups 1-3 will not be done at this clinic.

Group 4 will get VRC01 and Group 5 will get VRC01LS. Each group will get one IV infusion at their first visit.

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

We have no say in whether you are in Group 4 or 5. It will be random, like flipping a coin. You cannot change groups.

The IV infusion will take about 15 to 60 minutes. You will have to wait in the clinic for about a half hour after the infusion to see if there are any problems. Then for that night and for three more days, you will need to keep track of how you are feeling and if you have any symptoms. Contact the clinic staff if you have any issues or concerns after getting an infusion. If you have a problem, we will continue to check on you until it goes away.

12. In addition to giving you one of the antibodies, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you were born female;
- 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;

- Take urine and blood samples.

If you were born female, we will test you at some visits for gonorrhea, chlamydia, trichomonas vaginalis, bacterial vaginosis, herpes simplex virus, and yeast. If you were born male, we will test you at some visits for gonorrhea, herpes simplex virus, and chlamydia.

We will give you your test results. If you need care, we will tell you about the care we can give you here. We will also tell you about care we can help you get elsewhere.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 30 mL and 150 mL (about 2 tablespoons to a little more than a ½ 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 G, 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 review the results of these 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 also collect semen, rectal fluid and tissue, cervical fluid and cervical and vaginal tissue samples from you.

We want to see if the antibodies get to the parts of the body where people may be exposed to HIV: their rectum, vagina, and penis. We will take samples from these areas.

We will ask you to avoid some activities before we collect these samples. This will help make sure your samples give accurate lab readings. There are also some activities we will ask you to avoid after collecting the samples that are described below.

We will ask all participants born male to provide semen as well as rectal fluids and tissues. We will ask all participants born female to provide cervical fluids as well as cervical and vaginal tissues. If participants born female become

uncomfortable providing cervical fluids as well as cervical and vaginal tissues at any time we will ask you to provide rectal fluids and/or tissues instead.

Site: localize measurement units throughout the following sections as needed.

Semen collections (for persons born male)

You will provide semen at the clinic. We will ask you to ejaculate into a plastic cup, which we will give to you.

For the **2 days before** we collect your semen, we will ask you to follow these instructions:

- Do not ejaculate,
- Do not use anything with lubricants,
- Do not put saliva (your own or someone else's) on the penis,
- Do not receive oral sex.

Rectal fluid collections (for all participants)

We will collect rectal fluid by first placing a plastic tube about 2 cm wide (a little less than an inch) into your rectum. The tube will go in about 6½ cm (about 2½ inches). We will then place in your rectum either a small, absorbent sponge for 5 minutes or an absorbent balloon for less than a minute. The balloon will be inflated to the size of a chicken egg (2 x 1 inches, 5 x 3 cm) after it is inside your rectum and deflated before it is removed.

For the **2 days before** we collect your rectal fluid, we will ask you to follow these instructions:

- Do not have receptive anal intercourse
- Do not put anything into your anus, including cleaning products (creams, gels, lotions, pads, etc.), lubricant, enemas or douches (even with water)
- Do not use any anti-inflammatory creams in or around your anus.
- We will not collect rectal fluid if you are pregnant, or if we think you may have an anal or rectal infection. You should tell us if your rectal area is sore.

Rectal tissue collections (for all participants)

We will collect small samples of tissue about the size of a grain of rice from the lining of your rectum. These are called rectal biopsies. We will collect 2 biopsies at 5-7 different visits. To take the samples, we will place a plastic tube about 2 cm

wide (a little less than an inch) into the anus to view the lower part of the rectum. You may feel some discomfort, but the biopsies are almost always painless. It will take about 15 minutes.

You may see blood in your first few stools. This is normal after a biopsy. If you think the bleeding is excessive, contact your study clinician immediately.

For the **2 days before** we collect your rectal tissues, we will ask you to follow the same instructions as above. In addition, we will ask you to follow these instructions after the procedure:

- Do not have rectal sex and/or insert any foreign object or substance into the rectum for **5 days after** biopsy samples have been collected;

- You should call the clinic if you have a lot of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not getting better.

Cervical fluid collections (for persons born female)

You must have had a Pap smear within the last 3 to 5 years with the most recent result being normal. If you have not had a Pap smear within the last 3 years and would like to get one, we will tell you where you can get one.

We will collect cervical fluids by using either a soft sponge inserted into the opening of your cervix, or by using something call a menstrual cup inserted into your vagina. If we use a soft sponge to collect cervical fluids, we will insert a speculum (a device that holds your vagina open) into your vagina and place the sponge in the opening of the cervix. This is similar to getting a pap smear. If we use the menstrual cup, we will explain how to insert it into your vagina. You may insert it before you come to the clinic. You will wear it for up to 6 hours and remove it at the clinic. You will insert a second menstrual cup at the clinic and wear it for 10-15 minutes. If you are uncomfortable doing any of this on your own, you may come to the clinic and we will help you.

For the **2 days before** we collect your cervical fluid, we will ask you to follow these instructions:

- Do not use any spermicide, lubricants, douche (even with water), or medication in or around your vagina;

- Do not have vaginal intercourse or insert anything into your vagina;

- Using a vaginal ring for contraception is fine and can continue to be used. You will need to remove it for a few hours. The clinic staff can explain this to you.

We will not collect cervical fluid if you are menstruating or pregnant, or if we think you may have a cervical or vaginal infection. If you are menstruating, we may ask you to return to collect this sample at another time.

Cervical and vaginal tissue collections (for persons born female)

We will collect small samples of tissue about the size of a grain of rice. We will collect 2 cervical and 2 vaginal biopsies at 5-7 different visits. We will insert a speculum into your vagina. A speculum is a metal or plastic tool that looks like a bird's beak. It is used to help open your vagina a few inches.

After the speculum is put into your vagina, the cervix and vaginal wall will be cleaned with a clean cotton ball or swab.

Biopsies will be taken with clean forceps. Forceps are a metal or plastic tool to help get the tissue from inside your vagina and cervix. You may feel cramping, pain or discomfort. We will check to make sure that there is no bleeding from where the biopsies are taken. If there is bleeding, we will use a medication to stop it. One type of medication, silver nitrate, has a gray color. You may see gray flecks in your vaginal discharge after the biopsy. This is normal. The procedure will take about 15 minutes.

For the **2 days before** we collect your cervical/vaginal tissue, we will ask you to follow the same instructions as above. In addition, we will ask you to follow these instructions after the procedure:

- Do not have vaginal sex and/or insert any foreign object or substance, including tampons, into the vagina for **7 days after** biopsy samples have been collected;

- Participants should contact the clinic if they experience a large amount of bleeding, have a temperature of more than 38.1°C (100.5°F), experience chills, or have pain that is not improving.

- Using a vaginal ring for contraception is fine and can continue to be used.

14. We will counsel you on avoiding HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your risk of getting HIV low.

15. We will test your samples for this study.

We will send your samples (without your name) to labs approved by the HVTN for this study, which are located in the United States and South Africa. Researchers at these labs will test your samples to see how your immune system

responds to the antibodies. In rare cases, some of your samples may be sent to labs approved by the HVTN in other countries for research related to this study.

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

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

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

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

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

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

16. When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies by HVTN 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 part of your medical record. The studies are only being done for research purposes.

Will the HVTN sell my samples and information? No, but the HVTN 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. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN 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, sex, 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, vaccines, antibody mediated prevention, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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

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

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers

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

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

People who may see your information are:

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

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

17. 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 and its study monitors,
- The US Food and Drug Administration,
- South African Health Products Regulatory Authority (SAHPRA),

- [Insert name of local IRB/EC] ,
- Any regulatory agency that reviews clinical trials,
- The HVTN and people who work for them,
- The HVTN 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.

When the study is done, we may share the information from the study with others so they can see it and use it. We will not share any information that will let someone identify you.

18. We may take you out of the study at any time. We may do this even if you want to stay in the study.

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

19. We will stop most of your sample collections if you become pregnant during the study. We will continue blood draws to check your health.

We will encourage you to stay in the study if you choose. We will discuss your study options with you.

If you leave the study while you are still pregnant, we will contact you after your due date to ask some questions about your pregnancy and delivery.

20. If you get infected with HIV during the study, we will stop your study product administration, take fewer samples, and help you get care and support.

We will encourage you to stay in the study for up to 16 weeks if you choose. We will discuss your study options with you. We will counsel you about your HIV infection and about telling your partner(s). We will tell you where you can get support and medical care, and if there are other studies you may want to join. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

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:

In this study, we will take your blood. This can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of IV infusion procedure:

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 a blood clot or infection.

Risks of taking rectal and genital fluids and tissues:

We will ask you to stop some activities before and after we collect these samples. You may find this inconvenient. These sample collections may cause some anxiety, temporary discomfort, and embarrassment. We will try to make you as comfortable as possible.

All biopsies may cause a small amount of bleeding, which usually stops on its own. In rare cases, excess bleeding or infection may occur from a biopsy. If you need care, we will tell you about the care we can give you here. We will also tell you about care we can help you get elsewhere.

Until the areas where the biopsies were taken heal, you are at increased risk for HIV infection if you are exposed. Most people heal within 5 to 7 days, but some may take longer.

Personal problems/discrimination:

Some people who join HVTN 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. We do not expect you to test positive on HIV antibody tests. We have used several common HIV antibody tests to test samples of blood containing the antibodies and none of them detected the antibody.

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.

Although it has not been seen so far, getting VRC01 or VRC01LS may cause common HIV antibody tests to show that someone is HIV-negative, even if they are actually infected.

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 antibodies will increase, decrease, or not change your risk of becoming infected with HIV if exposed. If you get infected with HIV, we do not know how the antibodies might affect your HIV infection or how long it takes to develop AIDS.

We do not know how the antibodies will affect a pregnant participant or a developing baby.

Benefits

22. The study may not benefit you.

We do not know whether getting the antibodies might benefit you in any way. 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 help in the search for a vaccine to prevent HIV. However, if the antibodies later become approved and sold, 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 antibodies 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.

Next paragraph for Cape Town site only:

In this study, our clinic has insurance to cover your medical treatment in the case of a study-related injury, following 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 has 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 has limited funds to pay medical costs for study-related injuries that it determines are reasonable. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

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

You may disagree with the decision about whether your injury is study related. If you wish, the HVTN will ask independent experts 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].

South African sites, include the following paragraph:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Acting Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001
Tel: (012) 395 8126
Fax: (012) 395 9201
e-mail: portia.nkambule@health.gov.za

Your permissions and signature

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

27. In Section 16 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 keeps track of your decision about how your samples and information can be used.

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

OR

☐ I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐ I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

28. If you agree to join this study, you will need to sign or make your mark below. Before you sign or make your mark on this consent form, make sure of the following:

- You have read this consent form, or someone has read it to you.
- You feel that you understand what the study is about and what will happen to you if you join. You understand what the possible risks and benefits are.
- You have had your questions answered and know that you can ask more.

- You agree to join this study.

You will not be giving up any of your rights by signing this consent form.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix C Approved birth control methods (for sample informed consent form) for US sites

You should not become pregnant during the study because we do not know how the antibodies could affect the developing baby.

You must agree to use effective birth control from 21 days prior to enrollment through the last required protocol clinic visit.

Effective birth control means using any of the following methods every time you have sex:

- Birth control drugs that prevent pregnancy—given by 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 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 had your ovaries removed;
- You have a tubal ligation (your "tubes tied") or confirmed successful placement of a product that blocks the fallopian tubes;
- You are having sex only with a female partner or partners;
- You only have oral sex; or,
- You are sexually abstinent (no sex at all).

Remember: If you are having sex, you need to use male or female condoms to protect yourself from HIV infection.

If you join the study, we will test you for pregnancy at some visits, including before each study infusion.

Appendix D Approved birth control methods (for sample informed consent form) for South African sites

You should not become pregnant during the study because we do not know how the antibodies could affect the developing baby.

If you were born female and are sexually active in a way that could lead you to get pregnant, you must agree to use effective birth control, from 21 days before enrollment until your last study visit.

Effective birth control is defined as using 2 methods of birth control. :

ONE barrier contraceptive method:

- Male or female condoms; or,
- Diaphragm or cervical cap;

PLUS ONE of the following methods:

- Birth control drugs that prevent pregnancy—given by pills, injections, patches, vaginal rings, or inserts under the skin;
- Intrauterine device (IUD); or
- You are only having sex with a partner who has 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 had your ovaries removed;
- You have a tubal ligation (your "tubes tied") or confirmed successful placement of a product that blocks the fallopian tubes;
- You are sexually abstinent (no sex at all)

Sites may delete the bullets below, if desired.

- You are having sex only with a female partner or partners;
- You only have oral sex.

Remember: If you are having sex, you need to use male or female condoms to protect yourself from HIV infection.

Appendix E Sample consent form for use of samples and information in other studies

Title: A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

HVTN protocol number: HVTN 116

Site: [Insert site name]

When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies. 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 part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN sell my samples and information?

No, but the HVTN 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. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this..]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN 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, vaccines, antibody mediated prevention, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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

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

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it. Usually, no one would be able to look at your genome and link it to

you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small.

10. What are the risks of genetic testing?

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

U.S. Sites, include the following paragraph

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

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

People who may see your information are:

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

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

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact
[name and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact
[name and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact
[name/title/phone of person on IRB or other appropriate organization].

South African sites, include the following paragraph:

If you have questions about this trial you should first discuss them with your doctor or the ethics committee (contact details as provided on this form). After you have consulted your doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the South African Health Products Regulatory Authority (SAHPRA) at:

The Acting Chief Executive Officer
South African Health Products Regulatory Authority
Department of Health
Private Bag X828
PRETORIA
0001
Tel: (012) 395 8126
Fax: (012) 395 9201
e-mail: portia.nkambule@health.gov.za

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN keeps 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, vaccines, antibody mediated prevention, the immune system, and other diseases. This may include genetic testing and keeping my cells growing over time.

OR

☐ I agree to the option above *and* also to allow my extra samples combined with limited information to be used in genome wide studies.

OR

☐ I do not allow my extra samples to be used in any other studies. This includes not allowing genetic testing, growing more of my cells, or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time

Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time

For participants who are unable to read or write, a witness should complete the signature block below:

Witness's name (print)	Witness's signature	Date	Time

*Witness is impartial and was present for the consent process.

Appendix F Table of procedures (for sample informed consent form, Groups 1-3)

Group 1 and Group 2

Procedure	Screening visit	2 weeks before the first infusion visit	First infusion visit	Time after first infusion visit											
				1-2 weeks	5-6 weeks	8 weeks (2 months)	9-10 weeks	13-14 weeks	16 weeks (4 months)	19-20 weeks	24 weeks (6 months)	25-26 weeks	29-30 weeks	37-38 weeks	51-52 weeks (1 year)
IV Infusion			√			√			√		√				
Cervical fluid, rectal fluid, and semen samples		√		√	√		√	√		√		√	√	√	√
Cervical, vaginal, and rectal tissue samples		√										√	√	√	√
Genital and rectal infection testing	√							√				√			√
Medical history	√														
Complete physical	√														√
Brief physical		√	√	√	√	√	√	√	√	√	√	√	√	√	
Urine test	√			√										√	
Blood drawn	√	√		√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants born female)[a]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
HIV testing & pretest counseling	√											√		√	√
Risk reduction counseling	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Interview/ questionnaire	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pap smear (if needed)	√														

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out what products you received.

[a] Persons who had a both their ovaries removed (verified by medical records), are not required to have a pregnancy test.

Group 3

Procedure	Screening visit	2 weeks before the first infusion visit	First infusion visit	Time after first infusion visit										
				1-2 weeks	5-6 weeks	12 weeks (3 months)	15-16 weeks	24 weeks (6 months)	25-26 weeks	29-30 weeks	37-38 weeks	51-52 weeks (1 year)	64-65 weeks	76-77 weeks (1 1/2 years)
IV Infusion			√			√		√						
Cervical fluid, rectal fluid, and semen samples		√		√	√		√		√	√	√	√	√	√
Cervical, vaginal, and rectal tissue samples		√							√	√	√	√	√	(√)[b]
Genital and rectal infection testing	√						√		√			√		√
Medical history	√													
Complete physical	√													√
Brief physical		√	√	√	√	√	√	√	√	√	√	√	√	
Urine test	√			√									√	
Blood drawn	√	√		√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants born female)[a]	√	√	√	√	√	√	√	√	√	√	√	√	√	√
HIV testing & pretest counseling	√								√		√	√		√
Risk reduction counseling	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Interview/ questionnaire	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pap smear (if needed)	√													

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out what products you received.

[a] Persons who had both their ovaries removed (verified by medical records), are not required to have a pregnancy test.

[b] Cervical and vaginal biopsies will only be collected if the participant has missed prior collections.

Appendix G Table of procedures (for sample informed consent form, Groups 4-5)

Group 4

Procedure	Screening visit	Infusion visit	Time after infusion visit					
			1-2 weeks	5-6 weeks	9-10 weeks	13-14 weeks	19-20 weeks	25-26 weeks
IV Infusion		√						
Cervical fluid, rectal fluid, and semen samples	√		√	√	√	√	√	√
Cervical, vaginal, and rectal tissue samples			√	√		√	√	√
Genital and rectal infection testing	√					√		√
Medical history	√							
Complete physical	√							√
Brief physical		√	√	√	√	√	√	
Urine test	√		√				√	
Blood drawn	√	√	√	√	√	√	√	√
Pregnancy test (participants born female)[a]	√	√	√	√	√	√	√	√
HIV testing & pretest counseling	√					√		√
Risk reduction counseling	√	√	√	√	√	√	√	√
Interview/ questionnaire	√	√	√	√	√	√	√	√
Pap smear (if needed)	√							

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out what products you received.

[a] Persons who had both their ovaries removed (verified by medical records), are not required to have a pregnancy test.

Group 5

Procedure	Screening visit	Infusion visit	Time after infusion visit							
			1-2 weeks	5-6 weeks	9-10 weeks	13-14 weeks	19-20 weeks	25-26 weeks	37-38 weeks	51-52 weeks (1 year)
IV Infusion		√								
Cervical fluid, rectal fluid, and semen samples	√		√	√	√	√	√	√	√	√
Cervical, vaginal, and rectal tissue samples			√	√		√	√	√	√	√
Genital and rectal infection testing	√					√		√		√
Medical history	√									
Complete physical	√									√
Brief physical		√	√	√	√	√	√	√	√	
Urine test	√		√						√	
Blood drawn	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants born female)[a]	√	√	√	√	√	√	√	√	√	√
HIV testing & pretest counseling	√					√		√	√	√
Risk reduction counseling	√	√	√	√	√	√	√	√	√	√
Interview/ questionnaire	√	√	√	√	√	√	√	√	√	√
Pap smear (if needed)	√									

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out what products you received.

[a] Persons who had both their ovaries removed (verified by medical records), are not required to have a pregnancy test.

Appendix H Laboratory procedures for Group 1 and Group 2

Procedure	Ship to[1, 2]	Assay location[2]	Tube Type[4]	Tube size (vol. capacity)[4]	Visit: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
					Day: Screening visit[3]	D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183[15]	D197-211[15]	D253-267[15]	D351-365[15]	D442-456	D526-540	
					Week:	W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
							Inf #1			Inf #2					Inf #3		Inf #4							
BLOOD COLLECTION																								
Screening/Diagnostic																								
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HSV-1/2	Local lab	Local lab	SST	5mL	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[8]	UW-VSL/ HSML-NICD	UW-VSL/ HSML-NICD	EDTA	10mL	—	—	—	—	—	—	—	—	—	—	—	—	—	10	—	10	20	—	—	**40**
Safety Labs[21]																								
CBC/ Diff / platelets	Local lab	Local lab	EDTA	5mL	5	—	—	5	—	—	5	—	—	—	—	5	—	5	—	5	—	—	—	**30**
Chemistry panel[5]	Local lab	Local lab	SST	5mL	5	—	—	5	—	—	5	—	—	—	—	5	—	5	—	5	—	—	—	**30**
Hormone Levels																								
Hormone panel[16]	Local lab	Local lab	SST	8.5mL	—	8.5	—	—	—	—	—	—	—	—	—	—	—	8.5	8.5	8.5	8.5	—	—	**43**
STI Serology												—		—								—	—	
Syphilis[10]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Drug Levels/Detection																								
VRC01 Ab levels	CSR	NVITAL/FHCRC	SST	8.5mL	—	y	—	y	y	y	y	—	y	—	y	y	y	y	y	y	y	—	—	**0**
Immunogenicity Assays																								
Host genetics[6]	CSR	FHCRC	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0**
Anti-VRC01 Ab levels	CSR	VRC/NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	—	—	y	—	—	y	—	—	**0**
Functional humoral assays[9]	CSR	Duke	SST	8.5mL	—	y	—	y	y	—	y	—	y	—	—	y	—	y	y	y	y	—	—	**0**
STORAGE																								
Serum storage	CSR	—	SST	8.5mL	—	76.5	—	51	51	8.5	51	—	51	—	8.5	51	8.5	51	51	51	51	—	—	**561**
PBMC storage	CSR	—	ACD	8.5mL	—	51[W]	—	—	—	—	34[W]	—	—	—	—	34[W]	—	—	—	—	34[W]	—	—	**153**
Visit total					**25**	**151**	**0**	**61**	**51**	**9**	**95**	**0**	**51**	**0**	**9**	**95**	**9**	**90**	**70**	**90**	**124**	**0**	**0**	**927**
56-Day total[16]					**25**	**176**	**176**	**237**	**288**	**121**	**216**	**155**	**206**	**206**	**163**	**250**	**112**	**193**	**263**	**159**	**124**	**0**	**0**	
URINE COLLECTION																								
Urine dipstick[17, 21]	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	
Pregnancy Test[7, 21]	Local lab	Local lab			X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
RECTAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
CERVICAL/VAGINAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Trichomonas vaginalis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Bacterial vaginosis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Yeast[13]	Local lab	Local lab			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
MUCOSAL BIOPSY COLLECTION[14]																								
Colorectal																								**Total Biopsies**
VRC01 Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	3	—	—	—	—	—	—	—	—	—	—	—	3	3	3	3	—	—	
Visit total colorectal biopsies[19]					**0**	**5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**5**	**5**	**5**	**5**	**0**	**0**	**25**
Cervical																								
VRC01 Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	2	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	
Visit total cervical biopsies[19]					**0**	**4**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**	**2**	**2**	**2**	**0**	**0**	**14**
Vaginal																								
VRC01 Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	3	—	—	—	—	—	—	—	—	—	—	—	3	3	3	(3)[20]	—	—	
Visit total vaginal biopsies[19]					**0**	**5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**5**	**5**	**5**	**2 [(5)[20]]**	**0**	**0**	**22**
MUCOSAL SECRETION COLLECTION[14]																								
Semen	CSR	VRC/Duke			—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	
Cervical Secretions	CSR	VRC/Duke			—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	
Rectal Secretions	CSR	VRC/Duke			—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	

Footnotes:

Grayed out visits are not applicable to this group

[1] CSR = central specimen repository

[2] HVTN Laboratory Program includes laboratories at UW-VSL, FHCRC, Duke, NVITAL, VRC, CHIL, and HSML-NICD. 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); VRC = Vaccine Research Center (Bethesda, Maryland, USA); CHIL = Cape Town HVTN Immunology Laboratory (Cape Town, South Africa); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa).

[3] Screening may occur over the course of several contacts/visits up to and including day -14 prior to biopsy collection.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

[7] Pregnancy test may be performed on blood specimens. Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

[8] At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.12), blood should be drawn for HIV diagnostic testing, as shown for visit 17 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.14).

[9] Functional humoral assays may include nAb, ADCC, virion capture, and phagocytosis assays.

[10] Syphilis testing will be done by serology.

[11] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[12] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[13] Cervical/vaginal swabs will be collected from females for yeast only when clinically indicated.

[14] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP.

[15] Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[16] The total 56-day blood collection includes 10mL maximum blood loss per biopsy collection visit.

[17] And microscopy if needed.

[18] Hormone panel (persons born female only) is defined in Sections 9.3 (enrollment visits) and 9.5 (follow-up visits).

[19] The visit total indicates the total number of colorectal, cervical, or vaginal biopsies collected per visit.

[20] These biopsies will only be collected if the participant has missed prior collection visit(s), in order to maintain the overall number of biopsies in the "Total Biopsies" column.

[21] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

w = 5 x 1mL aliquots of ACD plasma will be harvested for storage during PBMC processing; no separate blood draw is needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, anti-VRC01 Ab level, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

TBD = to be determined.

Appendix I Laboratory procedures for Group 3

Procedure	Ship to[1, 2]	Assay location[2]	Tube Type[4]	Tube size (vol. capacity)[4]	Visit: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
					Day: Screening visit[3]	D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183[15]	D197-211[15]	D253-267[15]	D351-365[15]	D442-456[15]	D526-540[15]	
					Week:	W–2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
							Inf #1					Inf #2					Inf #3							
BLOOD COLLECTION																								
Screening/Diagnostic																								
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HSV-1/2	Local lab	Local lab	SST	5mL	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[8]	UW-VSL/ HSML-NICD	UW-VSL/ HSML-NICD	EDTA	10mL	—	—	—	—	—	—	—	—	—	—	—	—	—	10	—	10	10	—	20	**50**
Safety Labs[21]																								
CBC/ Diff / platelets	Local lab	Local lab	EDTA	5mL	5	—	—	5	—	—	—	—	—	5	—	—	—	5	—	—	—	5	—	**25**
Chemistry panel[5]	Local lab	Local lab	SST	5mL	5	—	—	5	—	—	—	—	—	5	—	—	—	5	—	—	—	5	—	**25**
Hormone Levels																								
Hormone panel[18]	Local lab	Local lab	SST	8.5mL	—	8.5	—	—	—	—	—	—	—	—	—	—	—	8.5	8.5	8.5	8.5	8.5	8.5	**60**
STI Serology																								
Syphilis[10]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Drug Levels/Detection																								
VRC01 LS Ab levels	CSR	NVITAL/FHCRC	SST	8.5mL	—	y	—	y	y	—	—	y	—	y	—	—	y	y	y	y	y	y	y	**0**
Immunogenicity Assays																								
Host genetics[6]	CSR	FHCRC	ACD	8.5mL	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0**
Anti-VRC01 LS Ab levels	CSR	VRC/NVITAL	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	—	—	y	—	—	—	—	y	**0**
Functional humoral assays[9]	CSR	Duke	SST	8.5mL	—	y	—	y	y	—	—	—	—	y	—	—	—	y	y	y	y	y	y	**0**
STORAGE																								
Serum storage	CSR	—	SST	8.5mL	—	76.5	—	51	51	—	—	8.5	—	51	—	—	8.5	51	51	51	51	51	51	**553**
PBMC storage	CSR	—	ACD	8.5mL	—	51[W]	—	—	—	—	—	—	—	34[W]	—	—	—	34[W]	—	—	—	—	34[W]	**153**
Visit total					**25**	**151**	**0**	**61**	**51**	**0**	**0**	**9**	**0**	**95**	**0**	**0**	**9**	**124**	**70**	**80**	**80**	**80**	**124**	**955**
56-Day total[16]					**25**	**176**	**176**	**237**	**288**	**112**	**112**	**60**	**60**	**155**	**104**	**104**	**104**	**132**	**202**	**149**	**80**	**80**	**124**	
URINE COLLECTION																								
Urine dipstick[17, 21]	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	
Pregnancy Test[7, 21]	Local lab	Local lab			X	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	
RECTAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	
CERVICAL/VAGINAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	
Trichomonas vaginalis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	
Bacterial vaginosis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	
Yeast[13]	Local lab	Local lab			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
MUCOSAL BIOPSY COLLECTION[14]																								
Colorectal																								**Total Biopsies**
VRC01 LS Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	1	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	1	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	3	—	—	—	—	—	—	—	—	—	—	—	3	3	3	3	3	3	
Visit total colorectal biopsies[19]					**0**	**5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**5**	**5**	**5**	**5**	**5**	**5**	**35**
Cervical																								
VRC01LS Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	(1)[20]	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	(1)[20]	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	2	—	—	—	—	—	—	—	—	—	—	—	2	—	—	—	—	—	
Visit total cervical biopsies[19]					**0**	**4**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**4**	**2**	**2**	**2**	**2**	**(2)[20]**	**16**
Vaginal																								
VRC01LS Ab levels	TBD	VRC/FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	(1)[20]	
IHC	TBD	FHCRC			—	1	—	—	—	—	—	—	—	—	—	—	—	1	1	1	1	1	(1)[20]	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	3	—	—	—	—	—	—	—	—	—	—	—	3	3	3	(3)[20]	(2-3)[20]	(2-3)[20]	
Visit total vaginal biopsies[19]					**0**	**5**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**5**	**5**	**5**	**2 [(5)[20]]**	**2 [(4-5)[20]]**	**(2-5)[20]**	**24**
MUCOSAL SECRETION COLLECTION[14]																								
Semen	CSR	VRC/Duke			—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	
Cervical Secretions	CSR	VRC/Duke			—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	
Rectal Secretions	CSR	VRC/Duke			—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	

Footnotes:

Grayed out visits are not applicable to this group

[1] CSR = central specimen repository

[2] HVTN Laboratory Program includes laboratories at UW-VSL, FHCRC, Duke, NVITAL, VRC, CHIL, and HSML-NICD. 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); VRC = Vaccine Research Center (Bethesda, Maryland, USA); CHIL = Cape Town HVTN Immunology Laboratory (Cape Town, South Africa); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa).

[3] Screening may occur over the course of several contacts/visits up to and including day -14 prior to biopsy collection.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

[7] Pregnancy test may be performed on blood specimens. Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

[8] At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.12), blood should be drawn for HIV diagnostic testing, as shown for visit 19 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.14).

[9] Functional humoral assays may include nAb, ADCC, virion capture, and phagocytosis assays.

[10] Syphilis testing will be done by serology.

[11] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[12] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[13] Cervical/vaginal swabs will be collected from females for yeast only when clinically indicated.

[14] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP.

[15] Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[16] The total 56-day blood collection includes 10mL maximum blood loss per biopsy collection visit.

[17] And microscopy if needed.

[18] Hormone panel (persons born female only) is defined in Sections 9.3 (enrollment visits) and 9.5 (follow-up visits).

[19] The visit total indicates the total number of colorectal, cervical, or vaginal biopsies collected per visit.

[20] These biopsies will only be collected if the participant has missed prior collection visit(s), in order to maintain the overall number of biopsies in the "Total Biopsies" column.

[21] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

w = 5 x 1mL aliquots of ACD plasma will be harvested for storage during PBMC processing; no separate blood draw is needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, anti-VRC01 Ab level, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

TBD = to be determined.

Appendix J Laboratory procedures for Group 4

Procedure	Ship to[1, 2]	Assay location[2]	Tube Type[4]	Tube size (vol. capacity)[4]	Visit: 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Total
					Day: Screening visit[3]	D-14	D0	D1-15	D29-43[15]	D56	D57-71	D84	D85-99[15]	D99-113	D112	D127-141[15]	D168	D169-183[15]	D197-211	D253-267	D351-365	D442-456	D526-540	
					Week:	W–2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
							Inf#1																	
BLOOD COLLECTION																								
Screening/Diagnostic																								
Screening HIV test	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HSV-1/2	Local lab	Local lab	SST	5mL	—	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics[8]	UW-VSL/ HSML-NICD	UW-VSL/ HSML-NICD	EDTA	10mL	—	—	—	—	—	—	—	—	10	—	—	—	—	20	—	—	—	—	—	30
Safety Labs[21]																								
CBC/ Diff / platelets	Local lab	Local lab	EDTA	5mL	5	—	—	5	—	—	—	—	—	—	—	5	—	—	—	—	—	—	—	15
Chemistry panel[5]	Local lab	Local lab	SST	5mL	5	—	—	5	—	—	—	—	—	—	—	5	—	—	—	—	—	—	—	15
Hormone Levels																								
Hormone panel[19]	Local lab	Local lab	SST	8.5mL	—	—	—	8.5	8.5	—	—	—	8.5	—	—	8.5	—	8.5	—	—	—	—	—	43
STI Serology																								
Syphilis[10]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
Drug Levels/Detection																								
VRC01 Ab levels	CSR	NVITAL/FHCRC	SST	8.5mL	—	—	y	y	y	—	y	—	y	—	—	y	—	y	—	—	—	—	—	0
Immunogenicity Assays																								
Host genetics[6]	CSR	FHCRC	ACD	8.5mL	—	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Anti-VRC01 Ab levels	CSR	VRC/NVITAL	SST	8.5mL	—	—	y	y	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	0
Functional humoral assays[9]	CSR	Duke	SST	8.5mL	—	—	y	y	y	—	y	—	y	—	—	y	—	y	—	—	—	—	—	0
STORAGE																								
Serum storage	CSR	—	SST	8.5mL	—	—	76.5	51	51	—	51	—	51	—	—	51	—	51	—	—	—	—	—	383
PBMC storage	CSR	—	ACD	8.5mL	—	—	51[W]	—	—	—	—	—	34[W]	—	—	—	—	34[W]	—	—	—	—	—	119
Visit total					**25**	**0**	**133**	**75**	**65**	**0**	**51**	**0**	**109**	**0**	**0**	**75**	**0**	**119**	**0**	**0**	**0**	**0**	**0**	**649**
56-Day total[16]					**25**	**25**	**158**	**232**	**297**	**272**	**190**	**116**	**224**	**224**	**160**	**234**	**75**	**193**	**193**	**0**	**0**	**0**	**0**	
URINE COLLECTION																								
Urine dipstick[17, 21]	Local lab	Local lab			X	—	—	X	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	
Pregnancy Test[7, 21]	Local lab	Local lab			X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	—	—	—	—	
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	
RECTAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	
CERVICAL/VAGINAL SWAB COLLECTION																								
Chlamydia/Gonorrhea[11]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	
Trichomonas vaginalis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	
Bacterial vaginosis[12]	Local lab	Local lab			X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	
Yeast[13]	Local lab	Local lab			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
MUCOSAL BIOPSY COLLECTION[14]																								
Colorectal																								Total Biopsies
VRC01 Ab levels	TBD	VRC/FHCRC			—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	—	—	—	—	
IHC	TBD	FHCRC			—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Visit total colorectal biopsies[20]					**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**10**
Cervical																								
VRC01 Ab levels	TBD	VRC/FHCRC			—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	—	—	—	—	
IHC	TBD	FHCRC			—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Visit total cervical biopsies[20]					**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**10**
Vaginal																								
VRC01 Ab levels	TBD	VRC/FHCRC			—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	—	—	—	—	
IHC	TBD	FHCRC			—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	—	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
Visit total vaginal biopsies[20]					**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**0**	**0**	**0**	**0**	**10**
MUCOSAL SECRETION COLLECTION[14]																								
Semen	CSR	VRC/Duke			X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	—	—	—	—	
Cervical Secretions	CSR	VRC/Duke			X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	—	—	—	—	
Rectal Secretions	CSR	VRC/Duke			X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	—	—	—	—	

Footnotes:

Grayed out visits are not applicable to this group

[1] CSR = central specimen repository

[2] HVTN Laboratory Program includes laboratories at UW-VSL, FHCRC, Duke, NVITAL, VRC, CHIL, and HSML-NICD. 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); VRC = Vaccine Research Center (Bethesda, Maryland, USA); CHIL = Cape Town HVTN Immunology Laboratory (Cape Town, South Africa); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa).

[3] Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion #1.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

[7] Pregnancy test may be performed on blood specimens. Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

[8] At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.12), blood should be drawn for HIV diagnostic testing, as shown for visit 14 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.14).

[9] Functional humoral assays may include nAb, ADCC, virion capture, and phagocytosis assays.

[10] Syphilis testing will be done by serology.

[11] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[12] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[13] Cervical/vaginal swabs will be collected from females for yeast only when clinically indicated..

[14] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP.

[15] Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[16] The total 56-day blood collection includes 5mL maximum blood loss per biopsy collection visit.

[17] And microscopy if needed.

[18] Mucosal secretion specimens will be collected as part of screening. They may be collected up to the infusion at visit 3.

[19] Hormone panel (persons born female only) is defined in Sections 9.3 (enrollment visits) and 9.5 (follow-up visits).

[20] The visit total indicates the total number of colorectal, cervical, or vaginal biopsies collected per visit.

[21] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

w = 5 x 1mL aliquots of ACD plasma will be harvested for storage during PBMC processing; no separate blood draw is needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, anti-VRC01 Ab level, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

TBD = to be determined.

Appendix K Laboratory procedures for Group 5

					Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	
					Day:	Screening visit[3]	D-14	D0	D1-15	D29-43[15]	D56	D57-71	D84	D85-99[15]	D99-113	D112	D127-141[15]	D168	D169-183[15]	D197-211	D253-267[15]	D351-365[15]	D442-456	D526-540	
					Week:	W–2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
							Inf#1																		
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**
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HSV-1/2	Local lab	Local lab	SST	5mL		—	—	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
HIV diagnostics[8]	UW-VSL/ HSML-NICD	UW-VSL/ HSML-NICD	EDTA	10mL		—	—	—	—	—	—	—	—	10	—	—	—	—	10	—	10	20	—	—	**50**
Safety Labs[21]																									
CBC/ Diff / platelets	Local lab	Local lab	EDTA	5mL		5	—	—	5	—	—	—	—	—	—	—	—	—	—	—	5	—	—	—	**15**
Chemistry panel[5]	Local lab	Local lab	SST	5mL		5	—	—	5	—	—	—	—	—	—	—	—	—	—	—	5	—	—	—	**15**
Hormone Levels																									
Hormone panel[19]	Local lab	Local lab	SST	8.5mL		—	—	—	8.5	8.5	—	—	—	8.5	—	—	8.5	—	8.5	—	8.5	8.5	—	—	**60**
STI Serology																									
Syphilis[10]	Local lab	Local lab	SST	5mL		5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**5**
Drug Levels/Detection																									
VRC01LS Ab levels	CSR	NVITAL/FHCRC	SST	8.5mL		—	—	y	y	y	—	y	—	y	—	—	y	—	y	—	y	y	—	—	**0**
Immunogenicity Assays																									
Host genetics[6]	CSR	FHCRC	ACD	8.5mL		—	—	z	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	**0**
Anti-VRC01LS Ab levels	CSR	VRC/NVITAL	SST	8.5mL		—	—	y	y	—	—	—	—	—	—	—	—	—	—	—	—	y	—	—	**0**
Functional humoral assays[9]	CSR	Duke	SST	8.5mL		—	—	y	y	y	—	y	—	y	—	—	y	—	y	—	y	y	—	—	**0**
STORAGE																									
Serum storage	CSR	—	SST	8.5mL		—	—	76.5	51	51	—	51	—	51	—	—	51	—	51	—	51	51	—	—	**485**
PBMC storage	CSR	—	ACD	8.5mL		—	—	51[W]	—	—	—	—	—	34[W]	—	—	—	—	34[W]	—	—	34[W]	—	—	**153**
Visit total						**25**	**0**	**133**	**75**	**65**	**0**	**51**	**0**	**109**	**0**	**0**	**65**	**0**	**109**	**0**	**85**	**119**	**0**	**0**	**832**
56-Day total[16]						**25**	**25**	**158**	**232**	**297**	**272**	**190**	**116**	**224**	**224**	**160**	**224**	**65**	**173**	**173**	**85**	**119**	**0**	**0**	
URINE COLLECTION																									
Urine dipstick[17, 21]	Local lab	Local lab				X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	
Pregnancy Test[7, 21]	Local lab	Local lab				X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	
Chlamydia/Gonorrhea[11]	Local lab	Local lab				X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
RECTAL SWAB COLLECTION																									
Chlamydia/Gonorrhea[11]	Local lab	Local lab				X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
CERVICAL/VAGINAL SWAB COLLECTION																									
Chlamydia/Gonorrhea[11]	Local lab	Local lab				X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Trichomonas vaginalis[12]	Local lab	Local lab				X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Bacterial vaginosis[12]	Local lab	Local lab				X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	
Yeast[13]	Local lab	Local lab				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
MUCOSAL BIOPSY COLLECTION[14]																									
Colorectal																									**Total Biopsies**
VRC01LS Ab levels	TBD	VRC/FHCRC				—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	2	1	—	—	
IHC	TBD	FHCRC				—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
					Visit total colorectal biopsies[20]	**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**2**	**2**	**0**	**0**	**14**
Cervical																									
VRC01LS Ab levels	TBD	VRC/FHCRC				—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	2	1	—	—	
IHC	TBD	FHCRC				—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
					Visit total cervical biopsies[20]	**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**2**	**2**	**0**	**0**	**14**
Vaginal																									
VRC01LS Ab levels	TBD	VRC/FHCRC				—	—	—	1	1	—	—	—	2	—	—	2	—	1	—	2	1	—	—	
IHC	TBD	FHCRC				—	—	—	1	1	—	—	—	—	—	—	—	—	1	—	—	1	—	—	
Infectivity	FHCRC/CHIL	FHCRC/CHIL				—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
					Visit total vaginal biopsies[20]	**0**	**0**	**0**	**2**	**2**	**0**	**0**	**0**	**2**	**0**	**0**	**2**	**0**	**2**	**0**	**2**	**2**	**0**	**0**	**14**
MUCOSAL SECRETION COLLECTION[14]																									
Semen	CSR	VRC/Duke				X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	
Cervical Secretions	CSR	VRC/Duke				X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	
Rectal Secretions	CSR	VRC/Duke				X[18]	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	

Footnotes:

Grayed out visits are not applicable to this group

[1] CSR = central specimen repository

[2] HVTN Laboratory Program includes laboratories at UW-VSL, FHCRC, Duke, NVITAL, VRC, CHIL, and HSML-NICD. 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); VRC = Vaccine Research Center (Bethesda, Maryland, USA); CHIL = Cape Town HVTN Immunology Laboratory (Cape Town, South Africa); HSML-NICD = HIV Sero-Molecular Laboratory, National Institute for Communicable Diseases (Johannesburg, South Africa).

[3] Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion #1.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment).

[6] Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline.

[7] Pregnancy test may be performed on blood specimens. Persons who are NOT of reproductive potential due to having undergone bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

[8] At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.12), blood should be drawn for HIV diagnostic testing, as shown for visit 17 above. If a participant has a confirmed diagnosis of HIV-infection, do not collect blood for HIV diagnostic testing (see Section 9.14).

[9] Functional humoral assays may include nAb, ADCC, virion capture, and phagocytosis assays.

[10] Syphilis testing will be done by serology.

[11] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[12] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[13] Cervical/vaginal swabs will be collected from females for yeast only when clinically indicated.

[14] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP.

[15] Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[16] The total 56-day blood collection includes 5mL maximum blood loss per biopsy collection visit.

[17] And microscopy if needed.

[18] Mucosal secretion specimens will be collected as part of screening. They may be collected up to the infusion at visit 3.

[19] Hormone panel (persons born female only) is defined in Sections 9.3 (enrollment visits) and 9.5 (follow-up visits).

[20] The visit total indicates the total number of colorectal, cervical, or vaginal biopsies collected per visit.

[21] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be collected.

w = 5 x 1mL aliquots of ACD plasma will be harvested for storage during PBMC processing; no separate blood draw is needed.

y = SST blood collected for serum storage will also cover specimen needs for the VRC01 drug level, anti-VRC01 Ab level, and functional humoral assays; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for host genetics assay; no separate blood draw is needed.

TBD = to be determined.

Appendix L Procedures at HVTN CRS for Group 1 and Group 2

Visit:	01[a]	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf1			Inf2					Inf3		Inf4							
Study procedures																				
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	—	—	—	—
Risk reduction counseling[b]	X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
Pregnancy prevention assessment[c]	X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
Behavioral risk assessment[d]	X	—	—	—	—	—	—	—	—	—	X	—	X	—	—	X	X	—	—	—
Confirm eligibility and obtain demographics	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Randomize[e]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
Social impact assessment questionnaire	—	—	—	—	—	X	—	—	—	—	—	—	X	—	—	—	X	—	—	—
Acceptability questionnaire	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	X	—	—	—
Concomitant medications	X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
Intercurrent illness/adverse experience	—	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
HIV infection assessment[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	X	X	—	—	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	—	—	—	X	—	X	—	—	X
Mucosal biopsy collection[g]																				
Colorectal	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	—	—	—
Cervical	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	—	—	—
Vaginal	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	—	—	—
Mucosal secretion collection[g]																				
Semen	—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	—
Cervical secretions	—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	—
Rectal secretions	—	X	—	X	X	—	X	—	X	—	—	X	—	X	X	X	X	—	—	—

Grayed out visits are not applicable to this group

[a] Screening may occur over the course of several contacts/visits up to and including visit 02, prior to biopsy collections.

[b] Includes transmission risk reduction counseling for HIV-infected participants.

[c] Pregnancy prevention assessment is required only for participants who were born female and are capable of becoming pregnant.

[d] Not applicable to HIV-infected participants.

[e] Participants will be randomized prior to the first infusion, ideally within 4 days. See Section 6.2.

[f] Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. If a participant has a confirmed diagnosis of HIV infection, do not perform HIV infection assessment.

[g] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP. Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

Procedures at HVTN CRS for Group 1 and Group 2 continued

Visit:	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf1			Inf2					Inf3		Inf4							
Local lab assessments[a]																				
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Syphilis, HBV, HCV	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HSV	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pap smear[b]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Blood hormone levels[c]	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	—	—	—
Urine collection																				
Urine dipstick	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Pregnancy (urine or serum HCG)[d]	X	X	X	X	X	X	X	—	X	—	X	X	X	X	X	X	X	—	—	—
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Safety labs[a]																				
CBC, differential	X	—	—	X	—	—	X	—	—	—	—	X	—	X	—	X	—	—	—	—
Chemistry panel	X	—	—	X	—	—	X	—	—	—	—	X	—	X	—	X	—	—	—	—
Rectal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Cervical/vaginal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Trichomonas vaginalis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Bacterial vaginosis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Yeast[g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Study product administration procedures[h]																				
IV infusion[i]	—	—	X	—	—	X	—	—	—	—	X	—	X	—	—	—	—	—	—	—
Reactogenicity assessments[j]	—	—	X	—	—	X	—	—	—	—	X	—	X	—	—	—	—	—	—	—

Grayed out visits are not applicable to this group

[a] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests will be collected (see Appendix H).

[b] Only for volunteers born female, per Sections 7.1 and 9.6. If collection of a pap smear is required, this may be done at any time provided the results are available prior to the collection of cervical samples.

[c] Only collected in persons born female.

[d] For a participant who was born female, pregnancy test must be performed on the day of every infusion and every biopsy prior to infusion or biopsy collections. Pregnancy test to determine initial eligibility will be performed at screening. Persons who are NOT of reproductive potential due to having undergone 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.

[e] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[f] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[g] Cervical/vaginal swabs will be collected from females for yeast only if clinically indicated.

[h] Not applicable to HIV-infected participants.

[i] 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 may be drawn within the 3 days prior to infusion.

[j] Reactogenicity assessments performed daily for at least 3 days postinfusion (see Section 9.10).

Appendix M Procedures at HVTN CRS for Group 3

Visit:	01[a]	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf1					Inf2					Inf3							
Study procedures																				
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	—	—
Risk reduction counseling[b]	X	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
Pregnancy prevention assessment[c]	X	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
Behavioral risk assessment[d]	X	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	X	—	X	—
Confirm eligibility and obtain demographics	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Randomize[e]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	X	—	—	X	—
Acceptability questionnaire	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	X	X	—
Concomitant medications	X	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
Intercurrent illness/adverse experience	—	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
HIV infection assessment[f]	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	X	X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	—	—	—	—	—	X	—	X	X	—	X
Mucosal biopsy collection[g]																				
Colorectal	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	X	X	—
Cervical	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	X	(X)h	—
Vaginal	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	X	(X)h	—
Mucosal secretion collection[g]																				
Semen	—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	—
Cervical secretions	—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	—
Rectal secretions	—	X	—	X	X	—	—	—	—	X	—	—	—	X	X	X	X	X	X	—

Grayed out visits are not applicable to this group

[a] Screening may occur over the course of several contacts/visits up to and including visit 02, prior to biopsy collections.

[b] Includes transmission risk reduction counseling for HIV-infected participants.

[c] Pregnancy prevention assessment is required only for participants who were born female and are capable of becoming pregnant.

[d] Not applicable to HIV-infected participants.

[e] Participants will be randomized prior to the first infusion, ideally within 4 days. See Section 6.2.

[f] Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

[g] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP. Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[h] These biopsies will only be collected if the participant has missed prior collection visit(s).

Procedures at HVTN CRS for Group 3 continued

Visit:	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf1					Inf2					Inf3							
Local lab assessments[a]																				
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Syphilis, HBV, HC	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HSV	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pap smear[b]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Blood hormone levels[c]	—	X	—	—	—	—	—	—	—	—	—	—	—	X	X	X	X	X	X	—
Urine collection																				
Urine dipstick	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	X	—	—
Pregnancy (urine or serum HCG)[d]	X	X	X	X	X	—	—	X	—	X	—	—	X	X	X	X	X	X	X	—
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Safety labs[a]																				
CBC, differential	X	—	—	X	—	—	—	—	—	X	—	—	—	X	—	—	—	X	—	—
Chemistry panel	X	—	—	X	—	—	—	—	—	X	—	—	—	X	—	—	—	X	—	—
Rectal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Cervical/vaginal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Trichomonas vaginalis[f]	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Bacterial vaginosis[f]	X	—	—	—	—	—	—	—	—	X	—	—	—	X	—	—	X	—	X	—
Yeast[g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Study product administration procedures[h]																				
IV infusion[i]	—	—	X	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—	—
Reactogenicity assessments[j]	—	—	X	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—	—

[a] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests will be collected (see Appendix I).
Grayed out visits are not applicable to this group
[b] Only for volunteers born female, per Sections 7.1 and 9.6. If collection of a pap smear is required, this may be done at any time provided the results are available prior to the collection of cervical samples.
[c] Only collected in persons born female.
[d] For a participant who was born female, pregnancy test must be performed on the day of every infusion and every biopsy prior to infusion or biopsy collections. Pregnancy test to determine initial eligibility will be performed at screening. Persons who are NOT of reproductive potential due to having undergone 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.
[e] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.
[f] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.
[g] Cervical/vaginal swabs will be collected from females for yeast only if clinically indicated.
[h] Not applicable to HIV-infected participants.
[i] 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 may be drawn within the 3 days prior to infusion.
[j] Reactogenicity assessments performed daily for at least 3 days postinfusion (see Section 9.10).

Appendix N Procedures at HVTN CRS for Group 4

Visit:	01[a]	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf#1																	
Study procedures																				
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	–	–	–	–	–	–	–	–
Risk reduction counseling[b]	X	–	X	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Pregnancy prevention assessment[c]	X	–	X	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Behavioral risk assessment[d]	X	–	–	–	–	–	–	–	X	–	–	–	–	X	–	–	–	–	–	–
Confirm eligibility, obtain demographics, randomize	X	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Social impact assessment	–	–	X	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Social impact assessment questionnaire	–	–	–	–	–	–	–	–	X	–	–	–	–	X	–	–	–	–	–	–
Acceptability questionnaire	–	–	–	–	X	–	–	–	–	–	–	X	–	X	–	–	–	–	–	–
Concomitant medications	X	–	X	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Intercurrent illness/adverse experience	–	–	X	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
HIV infection assessment[e]	–	–	–	–	–	–	–	–	X	–	–	–	–	X	–	–	–	–	–	–
Confirm HIV test results provided to participant	–	–	X	–	–	–	–	–	–	–	–	X	–	–	–	–	–	–	–	X
Mucosal biopsy collection[f]																				
Colorectal	–	–	–	X	X	–	–	–	X	–	–	X	–	X	–	–	–	–	–	–
Cervical	–	–	–	X	X	–	–	–	X	–	–	X	–	X	–	–	–	–	–	–
Vaginal	–	–	–	X	X	–	–	–	X	–	–	X	–	X	–	–	–	–	–	–
Mucosal secretion collection[g]																				
Semen	Xg	–	–	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Cervical secretions	Xg	–	–	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–
Rectal secretions	Xg	–	–	X	X	–	X	–	X	–	–	X	–	X	–	–	–	–	–	–

Grayed out visits are not applicable to this group

[a] Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

[b] Includes transmission risk reduction counseling for HIV-infected participants.

[c] Pregnancy prevention assessment is required only for participants who were born female and are capable of becoming pregnant.

[d] Not applicable to HIV-infected participants.

[e] Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

[f] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP. Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[g] Mucosal secretion specimens will be collected as part of screening. They may be collected up to the infusion at visit 3.

Procedures at HVTN CRS for Group 4 continued

Visit:	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf#1																	
Local lab assessments[a]																				
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Syphilis, HBV, HCV	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HSV	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pap smear[b]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Blood hormone levels[c]	—	—	—	X	X	—	—	—	X	—	—	X	—	X	—	—	—	—	—	—
Urine collection																				
Urine dipstick	X	—	—	X	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Pregnancy (urine or serum HCG)[d]	X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	—	—	—	—	—
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—
Safety labs[a]															—	—	—	—	—	
CBC, differential	X	—	—	X	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Chemistry panel	X	—	—	X	—	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Rectal swab collection															—	—	—	—	—	
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—
Cervical/vaginal swab collection															—	—	—	—	—	
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—
Trichomonas vaginalis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—
Bacterial vaginosis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	—	—	—	—
Yeast[g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Study product administration procedures[h]																				
IV infusion[i]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Reactogenicity assessments[j]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Grayed out visits are not applicable to this group

[a] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests will be collected (see Appendix J).

[b] Only for volunteers born female, per Sections 7.1 and 9.6. If collection of a pap smear is required, this may be done at any time provided the results are available prior to the collection of cervical samples.

[c] Only collected in persons born female.

[d] For a participant who was born female, pregnancy test must be performed on the day of infusion prior to infusion and on the day of every biopsy prior to biopsy collections. Pregnancy test to determine initial eligibility may be performed at screening, but must also be done on day 0 prior to first infusion. Persons who are NOT of reproductive potential due to having undergone 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.

[e] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[f] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[g] Cervical/vaginal swabs will be collected from females for yeast only if clinically indicated.

[h] Not applicable to HIV-infected participants.

[i] Blood draws required at the infusion visit 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 may be drawn within the 3 days prior to infusion.

[j] Reactogenicity assessments performed daily for at least 3 days postinfusion (see Section 9.10).

Appendix O Procedures at HVTN CRS for Group 5

Visit:	01[a]	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf#1																	
Study procedures																				
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	—	—	—	—
Risk reduction counseling[b]	X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Pregnancy prevention assessment[c]	X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Behavioral risk assessment[d]	X	—	—	—	—	—	—	—	X	—	—	—	—	—	—	X	X	—	—	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Social impact assessment questionnaire	—	—	—	—	—	—	X	—	—	—	—	—	—	X	—	—	X	—	—	—
Acceptability questionnaire	—	—	—	—	X	—	—	—	—	—	—	X	—	—	—	X	X	—	—	—
Concomitant medications	X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Intercurrent illness/adverse experience	—	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
HIV infection assessment[e]	—	—	—	—	—	—	—	—	X	—	—	—	—	X	—	X	X	—	—	—
Confirm HIV test results provided to participant	—	—	X	—	—	—	—	—	—	—	—	X	—	—	—	X	X	—	—	X
Mucosal biopsy collection[f]																				
Colorectal	—	—	—	X	X	—	—	—	X	—	—	X	—	X	—	X	X	—	—	—
Cervical	—	—	—	X	X	—	—	—	X	—	—	X	—	X	—	X	X	—	—	—
Vaginal	—	—	—	X	X	—	—	—	X	—	—	X	—	X	—	X	X	—	—	—
Mucosal secretion collection[g]															—					
Semen	Xg	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Cervical secretions	Xg	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Rectal secretions	Xg	—	—	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—

Grayed out visits are not applicable to this group

[a] Screening may occur over the course of several contacts/visits up to and including day 0 prior to infusion.

[b] Includes transmission risk reduction counseling for HIV-infected participants.

[c] Pregnancy prevention assessment is required only for participants who were born female and are capable of becoming pregnant.

[d] Not applicable to HIV-infected participants.

[e] Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

[f] Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the SSP. Mucosal biopsy collections must be at least 28 days from the previous biopsy collection

[g] Mucosal secretion specimens will be collected as part of screening. They may be collected up to the infusion at visit 3.

Procedures at HVTN CRS for Group 5 continued

Visit:	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	Post
Day:		D-14	D0	D1-15	D29-43	D56	D57-71	D84	D85-99	D99-113	D112	D127-141	D168	D169-183	D197-211	D253-267	D351-365	D442-456	D526-540	
Week:		W-2	W0	W1-2	W5-6	W8	W9-10	W12	W13-14	W15-16	W16	W19-20	W24	W25-26	W29-30	W37-38	W51-52	W64-65	W76-77	
Month:			M0			M2		M3			M4		M6							
Procedure	Scr.		Inf#1																	
Local lab assessments[a]																				
Screening HIV test	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Syphilis, HBV, HCV	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
HSV	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Pap smear[b]	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Blood hormone levels[c]				X	X				X			X		X		X	X		
Urine collection																				
Urine dipstick	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Pregnancy (urine or serum HCG)[d]	X	—	X	X	X	—	X	—	X	—	—	X	—	X	—	X	X	—	—	—
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Safety labs[a]																				
CBC, differential	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Chemistry panel	X	—	—	X	—	—	—	—	—	—	—	—	—	—	—	X	—	—	—	—
Rectal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Cervical/vaginal swab collection																				
Chlamydia/Gonorrhea[e]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Trichomonas vaginalis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Bacterial vaginosis[f]	X	—	—	—	—	—	—	—	X	—	—	—	—	X	—	—	X	—	—	—
Yeast[g]	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Study product administration procedures[h]																				
IV infusion[i]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Reactogenicity assessments[j]	—	—	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Grayed out visits are not applicable to this group

[a] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests will be collected (see Appendix K).

[b] Only for volunteers born female, per Sections 7.1 and 9.6. If collection of a pap smear is required, this may be done at any time provided the results are available prior to the collection of cervical samples.

[c] Only collected in persons born female.

[d] For a participant who was born female, pregnancy test must be performed on the day of infusion prior to infusion and on the day of every biopsy prior to biopsy collections. Pregnancy test to determine initial eligibility may be performed at screening, but must also be done on day 0 prior to first infusion. Persons who are NOT of reproductive potential due to having undergone 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.

[e] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal swabs in females; testing will occur at indicated visits and when clinically indicated.

[f] Cervical/vaginal swabs will be collected from females for bacterial vaginosis and Trichomonas vaginalis at the indicated visits and when clinically indicated.

[g] Cervical/vaginal swabs will be collected from females for yeast only if clinically indicated.

[h] Not applicable to HIV-infected participants.

[i] Blood draws required at the infusion visit 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 may be drawn within the 3 days prior to infusion.

[j] Reactogenicity assessments performed daily for at least 3 days postinfusion (see Section 9.10).

Appendix P Protocol Signature Page

A phase 1 clinical trial to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC-HIVMAB060-00-AB (VRC01) and VRC-HIVMAB080-00-AB (VRC01LS) in the serum and mucosa of healthy, HIV-uninfected adult participants

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Investigator of Record Name (print)	Investigator of Record Signature	Date

DAIDS Protocol Number: HVTN 116

DAIDS Protocol Version: HVTN 116, Version 2.0

Protocol Date: August 3, 2018