HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 128

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

DAIDS DOCUMENT ID 38523

IND 137719 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

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

STUDY PRODUCT(S) PROVIDED BY

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

September 18, 2018
FINAL
HVTN 128
Version 1.0

Contents

1 Ethical considerations

It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of 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 the prevention of HIV infection, using methods that are scientifically rigorous and valid, and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and/or other 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 vaccine and 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.

- 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.

- Participants who become HIV-infected during the trial are referred to medical practitioners to manage their HIV infection and to identify potential clinical trials they may want to join. If a program for antiretroviral therapy (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.

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 post study product administration and collecting information regarding side effects for several days post study product administration; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, study product administrations, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use (for persons assigned female sex at birth); 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 and 5 and 21 CFR 56.111 (a) 4 and 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 (see Section 9). Safety is monitored daily by HVTN clinical staff and routinely by the HVTN 128 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). The privacy of participants is protected by assigning unique identifiers in place of the participant’s name on study data and specimens. In the United States, research participants in HVTN protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data and Specimens with the HVTN. In some cases, a comparable confidentiality agreement process may be acceptable. 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 and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

Primary objective(s)

- To evaluate the safety and tolerability of VRC07-523LS administered at 10 mg/kg intravenous (IV) infusion every 4 months
- To evaluate the safety and tolerability of VRC07-523LS administered at 30 mg/kg IV infusion every 4 months
- To determine whether multiple infusions of VRC07-523LS reach and maintain detectable levels in the mucosa
- To correlate levels of VRC07-523LS in serum and the mucosa

Study products and routes of administration

- VRC07-523LS: VRC-HIVMAB075-00-AB (VRC07-523LS) is a human monoclonal antibody (mAb) targeted to the HIV-1 CD4 binding site. It was developed by the VRC/NIAID/NIH and manufactured under current Good Manufacturing Practice regulations at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc., Frederick, MD. VRC07-523LS will be supplied as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL.

Table 3-1 Schema

Group	N*	Route	VRC07-523LS Dose	Product administration schedule		
				D0	D112	D224
				W0	W16	W32
1	12	IV	10 mg/kg	X	X	X
2	12	IV	30 mg/kg	X	X	X
Total	24					

IV = intravenous infusion

N* = number of participants receiving at least one product infusion

Participants

24 healthy, HIV-1–uninfected volunteers aged 18 to 50 years; 24 study product recipients

Design

Multicenter, randomized, unblinded trial

Duration per participant

12 months of scheduled clinic visits followed by biopsy safety contact 2 weeks after the last scheduled clinic visit

Estimated total study duration

17 months (includes 5 months for enrollment, and 12 months of scheduled visits)

Investigational New Drug (IND) sponsor

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

Study product providers

- VRC07-523LS: 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 (Fred Hutch) (Seattle, Washington, USA)

Statistical and data management center (SDMC)

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

HIV diagnostic laboratory

University of Washington Virology Specialty Laboratory (UW-VSL) (Seattle, Washington, USA)

Endpoint assay laboratories

- Duke University Medical Center (Durham, North Carolina, USA)
- Fred Hutch/University of Washington (Seattle, Washington, USA)

- Vaccine Research Center – Immunology Testing Laboratory (Gaithersburg, Maryland, USA)

- Dartmouth College (Hanover, New Hampshire, USA)

Study sites

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

Safety monitoring

HVTN 128 PSRT; HVTN Safety Monitoring Board (SMB)

3.1 Protocol Team

Protocol leadership

Chair	Stephen Walsh Brigham & Women's Hospital 617-525-8418 swalsh@bwh.harvard.edu	*Statistician*	Ollivier Hyrien SCHARP, Fred Hutch 206-667-5780 ohyrien@fredhutch.org
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Other contributors to the original protocol

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	Lucio Gama VRC	*Clinical data manager*	Claire Chapdu SCHARP, Fred Hutch
Laboratory protocol operations manager	On Ho HVTN Laboratory Program, Fred Hutch	*Program and portfolio manager*	Lisel Koepl SCHARP, HVTN
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Clinic coordinator	Elvin Fontana-Martinez Brigham & Women's Hospital	*Statistical research associate*	Xue Han SCHARP, Fred Hutch
	Julie Czartoski Seattle CRS		
Community Advisory Board (CAB) members	Tasia Baldwin Seattle CAB	*Protocol development manager*	Ramey Fair HVTN Core, Fred Hutch
	Ray Allmond Cleveland CAB	*Community engagement unit representative*	Gail Broder HVTN Core, Fred Hutch
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	Justine Beck DAIDS, NIAID	*Technical editor*	Richa Chaturvedi HVTN Core, Fred Hutch

4 Background

4.1 Rationale for trial concept

Although the identification and implementation of diverse disease prevention strategies have decreased the number of newly diagnosed HIV infections, HIV/AIDS continues to be a global health burden. UNAIDS estimates that there were 1.8 million new HIV infections worldwide in 2017 (4). While many countries have made progress toward leveling HIV prevalence over the last few years, micro-epidemics of infection continue to occur in nearly all regions, even in countries possessing the full toolkit of proven prevention approaches (5-8). Furthermore, limitations of current methods and interventions including side effects, cost, and individual compliance highlight the importance of the development of a safe, effective, durable, and innovative biomedical option. Ultimately, an effective vaccine will be necessary to better control the HIV pandemic (9, 10).

An alternative approach to prevention and/or treatment of infectious diseases is passive administration of antibodies (Ab), 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 (11, 12) and for postexposure prophylaxis (PEP) against rabies, measles, varicella zoster, and other infectious diseases (13). Palivizumab, a mAb directed against the F protein of respiratory syncytial virus (RSV), has been used for more than 15 years to prevent RSV infection in high-risk infants (14).

Over the past several years, there has been a concerted and notably successful effort to isolate broadly neutralizing antibodies (bnAbs) against HIV-1 from chronically infected donors (15-31). Subsequent research has provided considerable insight into the sites these antibodies target on HIV-1 and their functionality (ie, the mechanisms by which they neutralize the virus) (18, 19, 28, 32). This research has informed efforts to design recombinant protein immunogens that can elicit such antibodies (33-36), prompting optimism that vaccines that elicit bnAbs against HIV-1 can be developed (34, 37). In addition, the availability of bnAbs against HIV opens the exciting possibility of antibody-mediated prevention (AMP) of HIV infection.

4.1.1 Rationale for mucosal sampling

Since the majority of HIV infections worldwide are the result of sexual exposure, the vagina/cervix, rectum/distal colon, or penis are crucial areas in the disease transmission process. The colon and cervix are lined by a columnar epithelium, which protects a large pool of potential HIV target cells, including 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%) (38-40).

The central role of mucosal sites in transmission and early infection underscores the need for prevention approaches that protect mucosal sites from infection. Humoral and cellular immune responses in mucosal compartments have been analyzed by the HVTN in vaccine trials as well as in recent and ongoing mAb trials.

Among the vaccine trials that have gathered data from mucosal samples were HVTN 069 and HVTN 076. During HVTN 069 (41), participants at the Seattle site were offered enrollment into a companion mucosal study. HVTN 076 was specifically designed to evaluate mucosal responses to the vaccine regimen of a large-scale phase 2b efficacy study that was being conducted in parallel, namely HVTN 505 (42). As it would have been challenging to perform in-depth mucosal evaluations within the framework and risk profile of the large-scale vaccine efficacy trial, a scientifically and operationally sound approach was to conduct a smaller scale study looking at the congruent intervention in a stringently designed phase 1 study that allowed the consistent evaluation of mucosal samples.

Similarly, in parallel with the large-scale efficacy AMP studies (HVTN 703/HPTN 081 and HVTN 704/HPTN 085) to assess whether a passively administered bnAb VRC01 can prevent HIV-1 infection in adults at risk, it is desirable to gather in-depth data on the distribution and persistence of bnAbs in mucosal secretions and tissues. In contrast to efficacy trials, where mucosal biopsies are not feasible to perform because of potential alterations in risk of infection due to the procedure itself, phase 1 studies present an opportunity to collect relevant data in human mucosal tissues. In HVTN 104, a phase 1 study that preceded the ongoing AMP studies (43), an ancillary study was created to obtain mucosal tissue samples from participants who received VRC01. Using Singulex technology, it was possible to detect VRC01 in sera, rectal secretions and biopsies, cervical secretions and vaginal biopsies at days 3-14 post 2nd/3rd infusions (see Figure 4-1). The antibody was functional and capable of providing increased resistance to Bal26 HIV-1 challenges (neutralization IC80 = 0.17 mcg/mL) in infused participants, but not in controls (Figure 4-2 preliminary data provided by J. McElrath, R. Astronomo and M. Lemos).

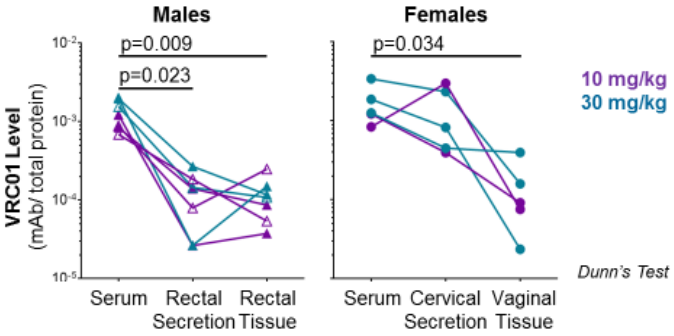

Figure 4-1 Levels of VRC01 in rectal and genital compartments of HVTN 104 participants collected 3-14 days post 2nd or 3rd infusion with 10 mg/kg (purple) or 30 mg/kg IV VRC01 antibody (teal). Significant differences were observed in comparisons between serum and rectal secretions, serum and rectal tissue, and serum and vaginal tissue. P values for comparisons based on Dunn's posthoc analysis are shown (Preliminary data provided by J. McElrath, R. Astronomo and M. Lemos).

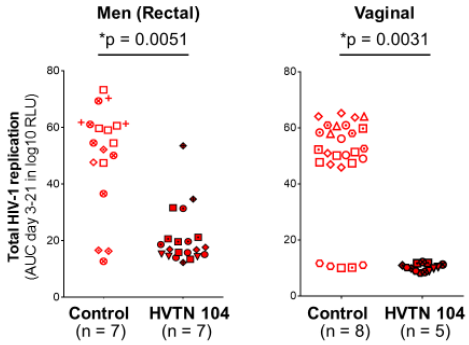

Figure 4-2 Ex-vivo explant infection of rectal and vaginal biopsies from HVTN 104 participants (collected 3-14 days post 2nd or 3rd infusion with 10 mg/kg or 30 mg/kg IV VRC01 antibody) or controls (not receiving infusions). Total HIV replication is measured by the nanoluciferase production of Bal26 HIV-1 on days 3-21 with $1x10^6$ viral particles. P value is Mann-Whitney test for the average of biopsies from a single donor (Preliminary data provided by J. McElrath, R. Astronomo and M. Lemos).

In HVTN 116 (NCT02797171), an ongoing trial in US and South African sites, mucosal secretion samples and biopsies are being obtained to compare serum, mucosal pharmacokinetics (PK), and functionality of VRC01 and VRC01LS across several infusions at multiple timepoints (see Table 4-1). HVTN 116 is a phase 1 multicenter, randomized, open-label trial. It was designed to evaluate the safety, pharmacokinetics, and anti-viral activity of VRC01 and VRC01LS in the serum and mucosa of healthy, HIV-uninfected adults. The study opened to accrual in March 2017, and as of May 15, 2018, 79 participants have been enrolled. There have been no safety pauses, no related Serious Adverse Events (SAEs), and product administrations have been generally well tolerated. Mucosal secretion sampling and biopsy procedures have also been generally well tolerated. The current mucosal biopsy collection schedule in HVTN 116 for Groups 1-3 is shown below in Table 4-2 and for Groups 4-5 in Table 4-3.

Table 4-1 HVTN 116 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	7	IV Infusion		IV Infusion		IV Infusion
Group 4	VRC01 30 mg/kg	16	IV Infusion				
Group 5	VRC01LS 30 mg/kg	10	IV Infusion				

Table 4-2 HVTN 116 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**	**5**	**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 4-3 HVTN 116 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

Preliminary results from HVTN 116 indicate that functional antibody is detectable in mucosal compartments 2 and 6 weeks post-multiple infusions (VRC01 or VRC01LS in groups 1, 2, and 3 in Table 4-1). At baseline, rectal samples from all participants were susceptible to challenge with Bal26, 1086 and Du422.1 HIV-1 viral strains. After three infusions, *ex-vivo* challenges of rectal explants with Bal26 (neutralization IC80 = 0.17 mcg/mL) were partially protected from HIV-1 challenge, whereas *ex-vivo* challenges of rectal explants with HIV-1 1086 (neutralization IC80 = 3 mcg/mL) and Du422.1 (neutralization IC80 < 45 mcg/mL) were susceptible to infection (Figure 4-3 preliminary data provided by J. McElrath, R. Astronomo and M. Lemos). The inhibition of Bal26 replication waned over time.

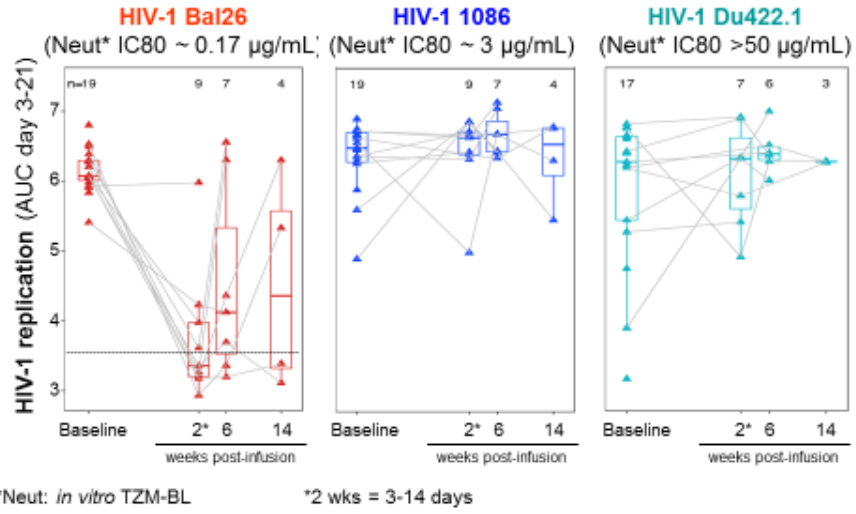

Figure 4-3 Ex-vivo explant infection of rectal biopsies from HVTN 116 participants collected at baseline, and weeks 2, 6, and 14 post third infusion of 10 mg/kg VRC01 IV, 30 mg/kg VRC01 IV or 30 mg/kg VRC01LS. Total HIV replication is measured by the nanoluciferase production of B.Bal26, 1086, or Du422.1 HIV-1 at days 3-21 post challenge. Triangles represent the mean of 1-3 biopsies per participant. Infusion arms are blinded at this stage of the trial (Preliminary data provided by J. McElrath, R. Astronomo and M. Lemos).

4.2 VRC07-523LS

The Vaccine Research Center (VRC), at the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes for Health (NIH), has developed several different HIV-1–specific mAb. Among them is VRC07-523LS, a highly potent and broadly neutralizing HIV-1 human mAb that targets the HIV-1 CD4 binding site. A similar antibody, VRC01, also targeting the CD4 binding site, is currently in clinical trials under IND 113,611 [prevention indication] and IND 126,001 and IND 126,664 [therapeutic indication]. VRC01 was originally isolated from a subject infected with HIV-1 for more than 15 years whose immune system controlled the virus without anti-retroviral therapy (44). Through advances in B-cell immunology, cloning, and structure-guided optimization techniques, numerous HIV-1 neutralizing mAbs, including VRC07 (“07” denotes sequential numbering when discovered), VRC07-523 (“523” denotes sequential numbering when engineered variant generated), and later VRC07-523LS (“LS” denotes 2 specific amino acid mutations), were isolated and subsequently engineered to have potency and breadth greater than those of antibodies identified earlier (45).

The VRC07 (wild-type) heavy chain was identified by 454 deep sequencing based on its similarity to the VRC01 mAb and paired with the VRC01 (wild-type) light chain (45). The engineered mutations that together define the 523 designation that increase the breadth and potency compared to VRC07 are a glycine to histidine

mutation at residue 54 of the heavy chain, a deletion of the first two amino acids, glutamate and isoleucine, from the light chain, and a valine to serine mutation at the third amino acid residue of the light chain (45). The LS mutation was introduced by site-directed mutagenesis and changed a methionine to leucine (L) and an asparagine to serine (S) (M428L/N434S, referred to as LS) in the C-terminus of the heavy chain constant region. The LS mutation increases the binding affinity for the neonatal Fc-receptor (FcRn), resulting in increased recirculation of functional IgG (46, 47), thus increasing plasma half-life.

In vitro, VRC07-523LS was found to be 5-to 8-fold more potent than VRC01 (see Figure 4-4), as well as broader, with an inhibitory concentration IC50 < 50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades, and an IC50 < 1 mcg/mL against 92% of HIV-1 viruses tested (45). Furthermore, VRC07-523LS displayed minimal levels of autoreactivity. VRC07-523LS was shown to have a prolonged half-life over VRC07 by about 2-fold (45) in non-human primates (NHPs).

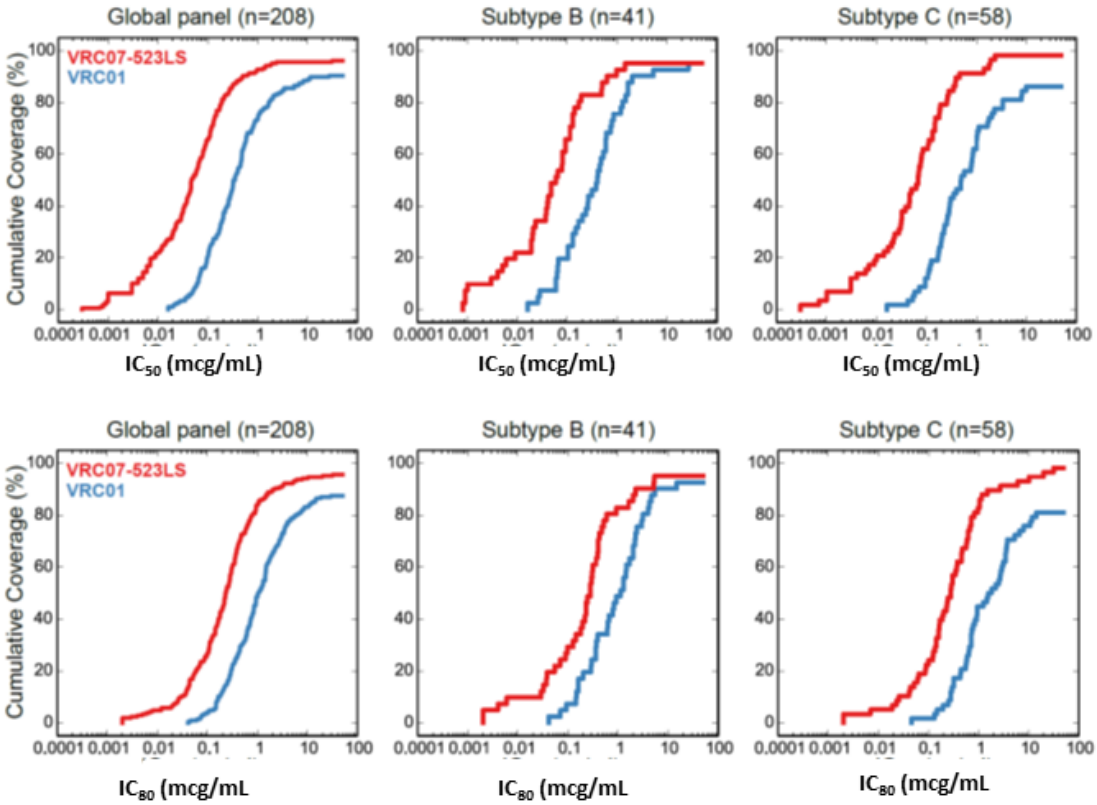

Figure 4-4 VRC07-523LS neutralizes a higher fraction of HIV-1 isolates at a lower concentration than VRC01 (data courtesy of Kshitij Wagh and Bette Korber).

4.2.1 Rationale for Testing VRC07-523LS

In vivo proof-of-concept studies have shown that VRC07-523LS is about 5-fold more potent than VRC01LS in Rhesus macaques at preventing SHIV infection following a mucosal challenge. VRC07-523LS has a longer half-life (9.8 days)

than VRC07 (4.9 days) following a single dose of mAb at 10 mg/kg administered by the IV route (45).

The increased neutralization potency *in vitro* and prolonged half-life of VRC07-523LS correlate with improved protection against SHIV infection *in vivo* in animal studies (Figure 4-5) suggesting a potential role for this bnAb for prevention of HIV-1 infection in humans (45).

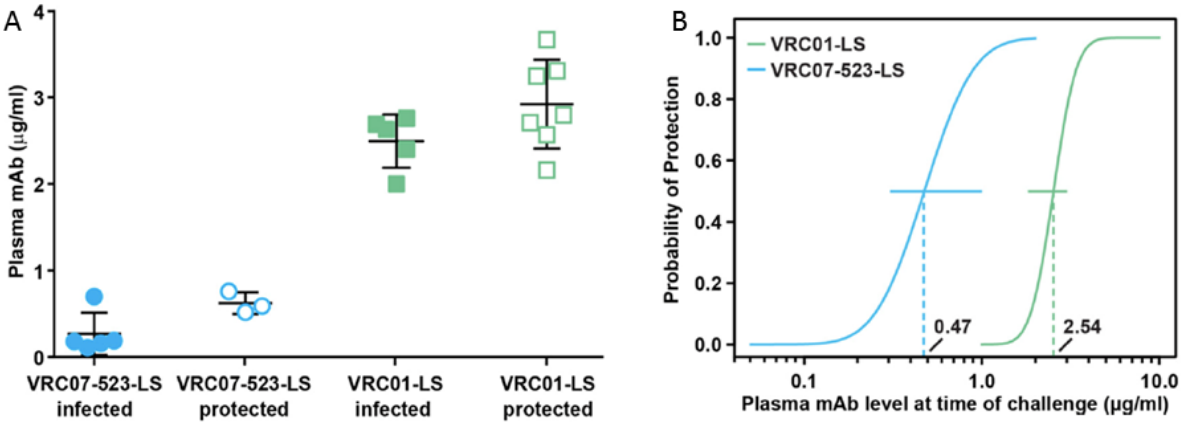

Figure 4-5 (A) Rhesus macaques were administered 0.2 mg/kg (n = 4) or 0.05 mg/kg (n = 4) of VRC07-523LS or 0.3 mg/kg of VRC01LS (n = 12), challenged with SHIV-BaLP4 intrarectally on day 5, and plasma concentrations of VRC07-523LS and VRC01LS were assayed by ELISA. (B) Regression model based on plasma mAb concentration at the time of infection (45).

When administered IV at a single dose of 10 mg/kg in cynomolgus macaques, the half-life of VRC07-523LS was about 12 days (Figure 4-6B), and it persisted at least 28 days (final collection point) in rectal and vaginal secretions and tissues (see the Investigator's Brochure (IB) for further details). When administered SC at a single dose of 10 mg/kg in rhesus macaques, the half-life of VRC07-523LS was about 14 days and it persisted at least 49 days (final collection point) in rectal, vaginal, and nasal secretions (see the IB for further details). Furthermore, complete protection from SHIV-SF162P3 challenge was demonstrated with a single dose of VRC07-523LS at 20 mg/kg administered IV. (Figure 4-6A). See the IB for further details.

(A) VRC07-523LS (20 mg/kg IV) **(B) VRC07-523LS (10 mg/kg IV)**

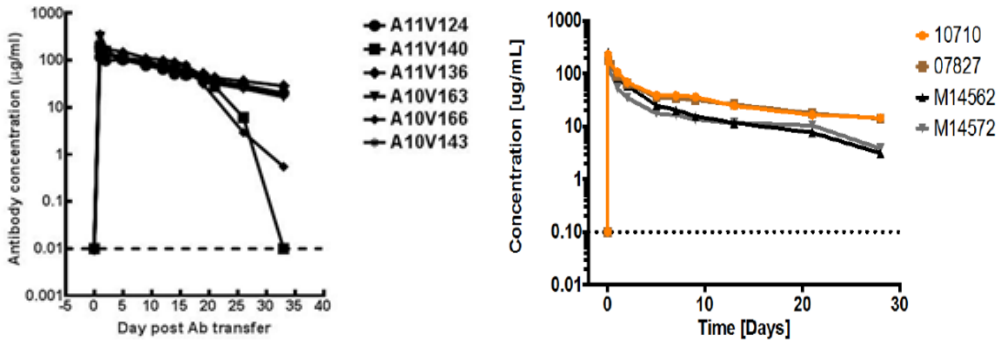

Figure 4-6 (A) VRC07-523LS was administered to male (n = 3) and female (n = 3) rhesus macaques at a dose of 20 mg/kg IV in a SHIV challenge study. (B) VRC07-523LS PK was measured in male (n = 2) and female (n = 2) cynomolgus macaques following a single administration of 10 mg/kg IV. Plasma concentrations were monitored by ELISA in both studies.

Repeated administration of VRC07-523LS will permit further understanding of the mucosal antibody levels, their accumulation after repeated dosing, and the consequences of any antidrug responses, if they were to develop.

4.3 Trial design rationale

Given that HIV-1 is acquired through sexual exposure, the concentration and function of antibodies 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 VRC01 and VRC01LS antibody levels in human mucosal secretions, there are no data on mucosal VRC07-523LS antibody levels or distribution in human mucosal tissues. Hence, this study presents a crucial opportunity to examine VRC07-523LS levels in both mucosal secretions and tissues.

The HVTN 127/HPTN 087 trial, which opened in February, 2018, is planned to enroll a total of 100 healthy, HIV-uninfected adult participants who will receive multiple injections of VRC07-523LS administered via the IV or SC routes. HVTN 127/HPTN 087, version 2.0 dated March, 2018 includes an IM arm with 24 participants, of whom 20 will receive VRC07-523LS, and 4 placebo, and shortens the interval of infusions to four months for all doses (Table 4-4). The primary objectives of the study are to assess safety and tolerability of repeated IV, SC, or IM administrations of VRC07-523LS, and to characterize serum levels over time for different doses, schedules, and routes and methods of administration. Additional objectives include building a population PK model of VRC07-523LS, and determining whether antidrug antibodies (ADA) emerge in response to repeated administrations of the antibody.

Table 4-4 HVTN 127/HPTN 087 amended schema

Group	N	Route	Dose	Product administration schedule				
				W0	W16	W32	W48	W64
1	20	IV	2.5 mg/kg	X	X	X	X	X
2	20	IV	5 mg/kg	X	X	X	X	X
3	20	IV	20 mg/kg	X	X	X	X	X
4	20	SC	2.5 mg/kg	X	X	X	X	X
5	20	SC	5 mg/kg	X	X	X	X	X
6	20	IM	2.5 mg/kg	X	X	X	X	X
	4		Placebo	X	X	X	X	X
Total	124							

IV = intravenous infusion
SC = subcutaneous injection
IM = intramuscular injection
All groups to enroll simultaneously.

In parallel with the HVTN 127/HPTN 087 trial, it is desirable to gather in-depth data on the distribution and persistence of VRC07-523LS in mucosal secretions and tissues when delivered by IV infusion. The HVTN 128 mucosal study will investigate concentrations and distribution of the VRC07-523LS antibody in mucosal tissues that are common sites of HIV exposure, and compare these to paired serum levels. This mucosal study can help us in understanding the underlying biological tenets of AMP, particularly with respect to mucosal challenge.

A critical aspect of the VRC07-523LS mucosal study will be the collection of mucosal secretions and tissues in all participants. Collections will include serum, rectal secretions and biopsies in men and women; cervicovaginal secretions as well as cervical and vaginal biopsies in women, and semen from men. The proposed time points will provide the opportunity to estimate VRC07-523LS peak and trough levels and accumulation. The mucosal specimens will be collected as outlined in Table 9-1 and Table 9-2.

To correlate VRC07-523LS levels in secretions and sera, we plan to assess VRC07-523LS levels in secretions and sera at peak and trough timepoints (Table 9-1 and Table 9-2). The genital and rectal secretion and biopsy sampling at baseline is designed to evaluate participant anatomical suitability for biopsy collections, before they have received their first VRC07-523LS administration. Baseline biopsies and secretions will be used as negative controls in the comparisons of VRC07-523LS levels post product administration. Serum collections will also serve to test anti-drug antibodies (ADA) at these timepoints.

The collection of biopsies and secretions after mAb delivery will serve to assess and compare biodistribution in mucosal compartments at the different mAb doses

at peak and trough timepoints. These timepoints were selected to evaluate the similarity and differences between VRC07-523LS and VRC01LS kinetics (Figure 4-7 A and B). Lastly, a collection at 16 weeks following last mAb administration (W48) will serve to assess the possibility of increased dosing intervals of VRC07-523LS.

4.3.1 Dose, route, and schedule

The VRC07-523LS doses and intervals in this trial are based on human studies of VRC01 (43, 48) and VRC01LS (49), preclinical and clinical studies of VRC07-523LS. The data collected in the proposed study could be combined with the data obtained in VRC 605 and in other trials of VRC07-523LS, including HVTN 127/HPTN 087, to further inform population PK modeling of VRC07-523LS in both serum and mucosal sites as described in section 6.4.4.1. The doses were chosen to increase the likelihood of detection of the mAb in the mucosal biopsy and secretion samples. The IV route is necessary to deliver these higher doses given the concentration of the mAb.

The rationale for the doses in this trial is also supported by serum PK data from the initial VRC01LS trials. The repeated doses of 10 mg/kg and 30 mg/kg have been used in HVTN 116 for the detection of mucosal VRC01 and VRC01LS, and have shown partial protection against Bal26 in rectal tissue infectivity assays at weeks 2-14 (Figure 4-3). This suggests those antibodies can reach the mucosa and have detectable functionality. As VRC01LS has less potency and breadth than VRC07-523LS, we have extended the assessment to 16 weeks, to evaluate the trough of a triannual dosing schedule.

4.4 Plans for future product development and testing

HVTN 128 is the next step in the characterization of VRC07-523LS. The information obtained is expected to inform further study of VRC07-523LS and its biodistribution in mucosal compartments. Additional upcoming Phase 1 trials plan to test VRC07-523LS as part of combination mAb regimens. As combinations of bnAbs targeting distinct regions of Env may be needed to successfully protect against sexual transmission of the diverse circulating strains of HIV-1, this information will contribute greatly to the design of future bnAb efficacy trials.

4.5 Preclinical safety studies of VRC07-523LS

4.5.1 *In vitro* safety studies

Several *in vitro* preclinical safety studies were performed with VRC07-523LS to assess potential off-target binding. To measure potential anti-phospholipid cross-reactivity, binding of VRC07-523LS to cardiolipin was assessed using an enzyme-linked immunosorbent assay (ELISA) and demonstrated minimal binding compared with 4E10, an earlier-generation HIV-1 specific mAb which binds

strongly to cardiolipin. VRC07-523LS was also tested for cross-reactivity against a panel of various nuclear antigens using a licensed systemic lupus erythematosus diagnostic test kit (Luminex AtheNA Multi-Lyte® ANA-II test) and did cross-react with a small subset of nuclear antigens consistent with some reactivity with nuclear antigens. In addition, VRC07-523LS was assessed for anti-phospholipid properties in a clinical activated partial thromboplastin time (aPTT) assay and compared to the anti-HIV mAbs 4E10 and VRC01 as well as palivizumab; only 4E10 showed evidence of antiphospholipid activity. By immunohistochemistry, VRC07-523LS displayed minimal binding to HEp-2 cells at 50 mcg/mL and no binding at 25 mcg/mL (45).

A tissue cross-reactivity (TCR) study was performed in accordance with "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies" to determine the potential cross-reactivity of VRC07-523LS with cryosections of human and Sprague-Dawley rat tissues. VRC07-523LS staining was similar between the human and rat tissues examined, although staining tended to be somewhat more intense and frequent in the human tissue compared to the Sprague-Dawley rat tissues. According to ICH S6(R1), mAb binding to cytoplasmic sites generally is considered of little to no toxicologic significance. See the IB for further details.

4.5.2 *In vivo* toxicology studies

4.5.2.1 Repeat dose IV and SC toxicity study in Sprague-Dawley rats

A repeat dose IV and SC toxicity study with VRC07-523LS was performed in male and female Sprague-Dawley rats in accordance with "Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies." Treatment with VRC07-523LS at doses up to 400 mg/kg/dose IV or 40 mg/kg/dose SC with three doses at 10 day intervals was generally well tolerated as most findings were reversible and no longer seen at the end of the recovery period. Additionally, histologic changes were not observed in the GLP repeat dose toxicology study in the cell types which had had staining observed in the GLP tissue cross reactivity (TCR) study. The no observed adverse effect levels (NOAELs) for this study were 400 mg/kg IV and 40 mg/kg SC. See the IB for further details.

4.5.2.2 Local tolerance of VRC07-523LS administered IM to Sprague-Dawley rats

A GLP local tolerance study (IITRI Project N0. 2749-001) was performed to evaluate tissue reactions of VRC-HIVMAB075-00-AB (VRC07-523 LS). Sprague-Dawley rats (five rats/sex in each group) were administered a single intramuscular (IM) injection of either the control (Final Formulation Buffer) or the mAb at a dose of 2.5 mg/kg on Day 1. Rats were then subjected to necropsy on Day 7 (6 days after dosing). Experimental endpoints included moribundity/mortality, daily clinical signs of toxicity, and injection site (Draize) reactogenicity scoring; body weights; plasma fibrinogen levels, serum alpha-2-macroglobulin (A2M) levels; gross pathology at necropsy; and microscopic pathology of the skeletal muscle injection sites.

No treatment-related findings were noted locally at the injection site through injection site reactogenicity observations, limb evaluations, and gross and microscopic pathology. No evidence of systemic toxicity was also noted following a single IM injection of the HIV mAb as there were no adverse clinical findings seen and no alterations in body weights and serum A2M levels. There were statistically significant changes in plasma fibrinogen levels in the mAb-treated group (compared to the controls); however, these findings were considered to be of minimal toxicological significance.

4.6 Preclinical PK and challenge studies of VRC07-523LS

In a SHIV challenge study, VRC07-523LS was administered to male (n = 3) and female (n = 3) rhesus macaques at a dose of 20 mg/kg IV and the plasma concentrations monitored by ELISA (Figure 4-6A). 6/6 animals were protected from SHIV-SF162P3 challenge on Day 5 after receiving a single dose of VRC07-523LS at 20 mg/kg IV. The average plasma concentration of VRC07-523LS on the day of the challenge was 114.2 mcg/mL. See the IB for further details.

An additional challenge study assessed whether the increased neutralization potency observed with VRC07-523LS *in vitro* would confer greater protection *in vivo* compared to VRC01LS. 7/12 male rhesus macaques were protected from SHIV-BaLP4 intrarectal challenge after receiving VRC01LS at 0.3 mg/kg IV, whereas 3/4 male rhesus macaques were protected after receiving VRC07-523LS at 0.2 mg/kg IV. VRC07-523LS showed a > 5-fold increase in potency compared to VRC01LS, consistent with its ability to better neutralize viruses *in vitro* (45).

4.7 Clinical studies of VRC07-523LS

4.7.1 VRC 605

A phase 1, dose-escalation study of VRC07-523LS, the VRC 605 protocol (NCT03015181), is currently underway in healthy, HIV-uninfected adults to evaluate the safety and pharmacokinetics of 1 to 3 administrations of the antibody. The doses being evaluated are a single administration of 1 mg/kg and 5 mg/kg IV and SC, and 20 mg/kg and 40 mg/kg IV, and three administrations (q3 months) of 5 mg/kg SC and 20 mg/kg IV VRC07-523LS (Table 4-5).

Table 4-5 VRC 605 study schema

Group	Participants	Administration Schedule		
		Day 0	Week 12	Week 24
1	4[#]	1 mg/kg IV		
2	3	5 mg/kg IV		
3	3	5 mg/kg SC		
4	3	20 mg/kg IV		
5	3	40 mg/kg IV		
6	5	5 mg/kg SC	5 mg/kg SC	5 mg/kg SC
7	5	20 mg/kg IV	20 mg/kg IV	20 mg/kg IV
Total	25			

[#] One participant enrolled into Group 1 then withdrew prior to receiving VRC07-523LS, so an additional participant was enrolled into the group.

Study objectives include evaluating the safety and tolerability of the study regimen and the pharmacokinetics of each dose level; determining the presence or absence of detectable ADA to VRC07-523LS; and evaluating for evidence of functional activity of VRC07-523LS.

As of January 15, 2018, the VRC 605 study is fully enrolled. Twenty-five (25) of 26 participants have received at least 1 dose of VRC07-523LS (12 SC and 25 IV administrations). One participant withdrew prior to receiving the study product. There have been no SAEs and no safety pauses for adverse events (AEs). Overall, 15 of 25 participants (60%) have had at least one AE, with the maximum severity being Grade 1 for 7 participants, Grade 2 for 6 participants, Grade 3 for 1 participant, and Grade 4 for 1 participant. The Grade 4 AE was for a drug induced liver injury likely caused by fluoxetine. This participant was independently evaluated by the NIH hepatology consult service and product administrations were discontinued due to the concomitant illness. While the participant was being followed for safety, her liver enzymes decreased, but then increased again after being started on citalopram, which reinforced that the original event was likely incited by an underlying sensitivity to selective serotonin reuptake inhibitor (SSRI) medications. Six (6) mild to moderate AEs were assessed as related to study product, including mild dizziness, mild abdominal pain, and 4 infusion reactions (1 mild and 3 moderate, reported for 2 participants). All AEs assessed as related to the study product have resolved without residual effects.

Two (2) participants developed infusion reactions shortly after IV product administration. Symptoms were typical of infusion reactions observed with other mAbs. No atypical symptoms or delayed symptoms were seen. One participant enrolled in the 40 mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. The participant was treated with acetaminophen and ibuprofen. All symptoms resolved within 12 hours. A separate participant in the 20 mg/kg IV group experienced infusion reactions (n = 2 moderate, n = 1 mild) after each product infusion. The participant experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia (mostly back), and arthralgia (mostly hips and knees). Symptoms began 15 minutes to 1 hour after completion of each product administration and completely resolved within 12 hours. The participant was

treated with acetaminophen and ibuprofen. Otherwise, product administrations have been generally well tolerated.

For solicited local reactions in the week after VRC07-523LS administrations, one of 17 participants (5.9%) who received the product by IV administration reported mild bruising at administration site, and 5 of 8 participants (62.5%) who received the product SC reported mild pain/tenderness at the injection site.

For solicited systemic AEs reported to have occurred within 3 days after product administration, 4 of 17 participants (23.5%) receiving VRC07-523LS IV reported mild or moderate systemic reactogenicity symptoms. The reported symptoms were malaise (n = 2 mild, n = 1 moderate), myalgia (n = 2 mild, n = 1 moderate), mild headache (n = 2), and moderate chills (n = 2). Five (5) of 8 participants (62.5%) receiving VRC07-523LS SC reported mild systemic reactogenicity symptoms: malaise (n = 3), myalgia (n = 2), headache (n = 3), chills (n = 1), nausea (n = 1), and joint pain (n = 2).

Figure 4-7 displays interim VRC07-523LS PK results in VRC 605.

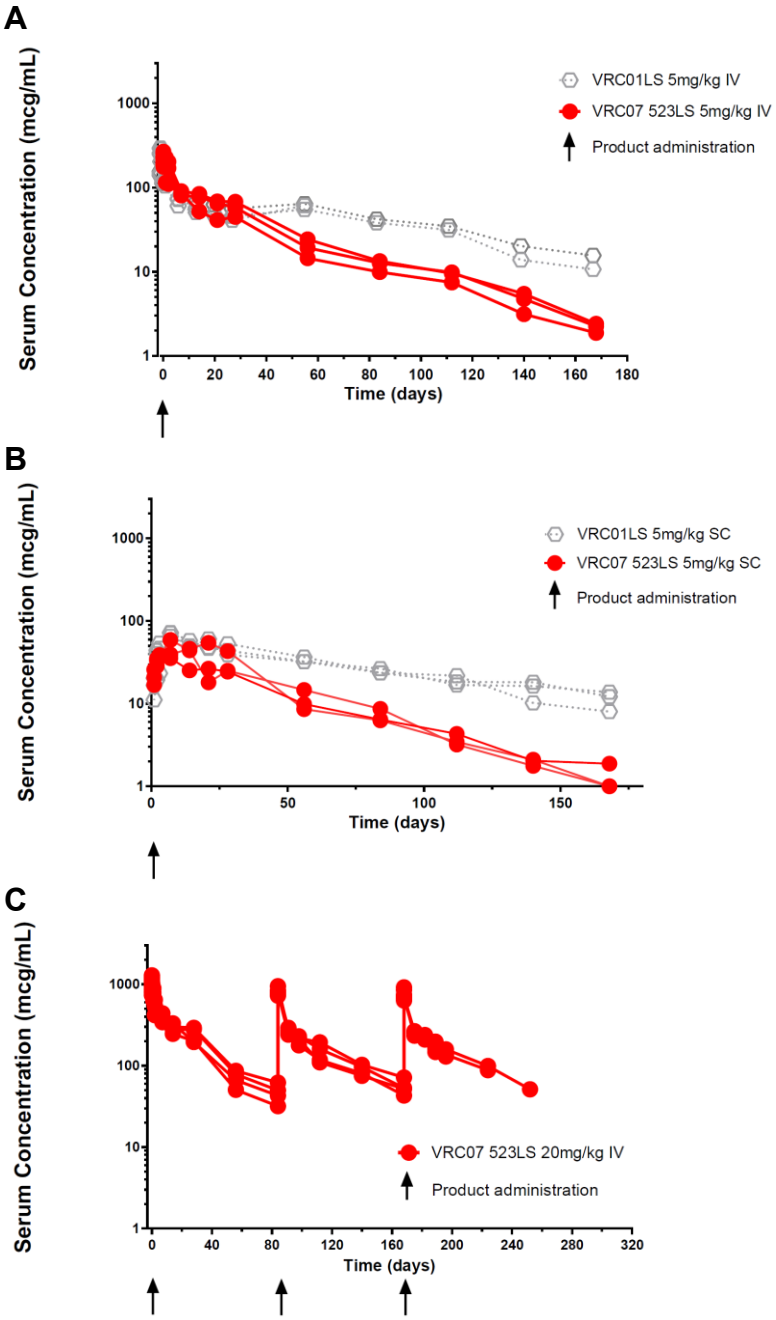

Figure 4-7. Interim VRC 605 PK results for VRC07-523LS with VRC01LS comparators. (A) Single administration of 5 mg/kg IV; all administrations completed. (B) Single administration of 5 mg/kg SC; all administrations completed. (C) Repeated administrations of 20 mg/kg IV every three months; all administrations completed. VRC07-523LS shows stable kinetics following repeat administrations.

4.7.2 HVTN 127/HPTN 087

As of July 31, 2018, 24 participants have been enrolled in the IV administration arms of HVTN 127/HPTN 087, 8 in Group 1 (2.5 mg/kg), 8 in Group 2 (5 mg/kg), and 8 in Group 3 (20 mg/kg). No SAEs and only one mild product-related AE (injection site pruritus in an SC recipient) have been identified to date.

4.8 Potential risks of study products and administration

There is limited human experience with administration of VRC07-523LS. VRC 605 was already evaluating VRC07-523LS prior to the start of HVTN 127/HPTN 087 and thus far there have been no SAEs or Grade 3 or higher related AEs in HVTN 127/HPTN 087. In addition, the similar CD4-binding site mAb VRC01 has been given to more than 3000 adults and 60 infants in several phase 1 and phase 2b clinical trials. More than 10,000 infusions of 10 mg/kg and 30 mg/kg VRC01 have been given to HIV-uninfected adults in HVTN 703/HPTN 081 [NCT02568215] and HVTN 704/HPTN 085 [NCT02716675]. Both VRC01 and VRC01LS are being tested in an ongoing phase 1 study (HVTN 116).

Standard infusion reactions to mAb administration are typically mild but may include fever, flushing, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, hypertension, pruritus, rash, urticaria, diarrhea, tachycardia or chest pain (50). Most infusion reactions appear to result from antibody-antigen interactions resulting in cytokine release (50). Administration of mAbs may have a risk of severe reactions, such as acute anaphylaxis, serum sickness, angioedema, bronchospasm, hypotension, and hypoxia, the generation of ADAs; they may also be associated with an increased risk of infections. However, these reactions are rare and more often associated with mAbs targeted to human proteins (50) or with the use of murine mAbs, which have a risk of eliciting human anti-mouse antibodies (51). Infusion of mAbs directed against cell surface targets on lymphocytes may cause a reaction known as “cytokine release syndrome”, with clinical manifestations including fatigue, headache, urticaria, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling, rhinitis, nausea, vomiting, flushing, fever, chills, hypotension, tachycardia, and asthenia (52). Cases of cytokine release syndrome occur most often in the first few hours after the first mAb dose, 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 (52).

Since VRC07-523LS targets a viral antigen rather than human cell surface antigens and is a human mAb, severe infusion reactions are expected to be rare.

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, characterized by urticaria, fever, lymph node enlargement, and joint pains. These symptoms may not appear until several days after the exposure to the mAb and are noted to be more common with chimeric types of mAb (51).

Reactions related to the rate of infusion have been described for several FDA-licensed mAbs. With licensed therapeutic mAbs, cytokine-mediated infusion reactions, including cytokine release syndrome, are typically managed by temporarily stopping the infusion, administering histamine blockers and restarting the infusion at a slower rate (53). Supportive treatment may also be indicated for some signs and symptoms.

To date, the clinical trial safety experience with VRC01-class mAbs has been reassuring:

- In HVTN 104, IV administration of VRC01 was generally well-tolerated with mild pain and/or tenderness commonly reported at the site of the IV infusion. Mild to moderate systemic reactogenicity symptoms were reported by VRC01 recipients following at least one of the infusions, but there was no clear relationship with frequency or severity to the dose of VRC01 (48).

- No hypersensitivity reactions or cytokine release syndrome symptoms were reported in HVTN 104 (48).

- The ongoing blinded HVTN 704/HPTN 085 and HVTN 703/HPTN 081 trials have reported an approximately 1% rate of urticaria or similar reactions.

- In the ongoing VRC 605 trial of VRC07-523LS, there have been no SAEs and no safety pauses. The maximum severity of related AEs has been Grade 1 (for 17 events) and Grade 2 (for 6 events, including 2 infusion reactions).

- Serious reactions associated with mAb administration, such as acute anaphylaxis, serum sickness, ADAs, and increased risk of infections have not been observed to date in trials of VRC01-class mAbs.

There is a possibility that receipt of the study product will cause a reactive result on some currently available HIV test kits, especially if testing occurs close to study product administration timepoints (see Section 9.7.1).

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 irritation (called phlebitis), or blood clot. Risk will be minimized by using sterile technique and universal precautions. Blood drawing may also cause anemia.

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 when it is inserted. This will be prevented through careful decontamination of local skin prior to catheter placement and through the use of infection control practices during infusion. Product contamination will be

prevented by the use of aseptic technique in the pharmacy and universal precautions during product administration.

Risks of biopsy and secretion collections: Collection of cervicovaginal secretions using menstrual cups or sponges can cause momentary discomfort during speculum or menstrual cup insertion and, in some cases, minor bleeding. Collection of rectal secretion samples using a rectal balloon sampling device can cause momentary discomfort during anoscope insertion and, in some cases, minor bleeding. Collection of semen can be embarrassing for the participant.

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 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 (in cervicovaginal tissue and within 3 days in rectal tissue) (54).

In the proposed schedule, a minimum of 21 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 300 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 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 (55). As the biopsies create superficial wounds in mucous membranes, healing is rapid. By 5-14 days, cervical healing is expected to be complete (54).

A review of 34 studies in which 8,330 cervical and vaginal biopsies were taken concluded that cervical and vaginal biopsies taken among special populations, including women living in high HIV prevalence areas, are also safe and well tolerated (56). As of May 15, 2018, HVTN 116 has conducted 472 rectal biopsy collections, 280 cervical biopsy collections and 339 vaginal biopsy collections in a total of 79 enrolled participants. One female could not undergo complete collections due to a vagal reaction after the first biopsy collection; one reported embarrassment after vaginal collection, and one stinging from silver nitrate. Two participants reported rectal discomfort after anoscope insertion but tolerated the collections. There have not been any terminations to date due to discomfort with the procedures. Cervical and vaginal biopsies in one female participant were permanently discontinued due to recurring vaginitis of unclear etiology.

Regarding procedure-related events during HVTN 116, to date there has been one pre-syncopal event after the collection of vaginal/cervical/rectal biopsies that

resolved on its own; one report of minimal rectal bleeding discovered when wiping with toilet paper that resolved on its own; two reports of constipation (one treated with medication and another resolved on its own), and one report of rectal pain that resolved on its own.

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objectives 1:

- To evaluate the safety and tolerability of VRC07-523LS administered at 10 mg/kg IV infusion every 4 months
- To evaluate the safety and tolerability of VRC07-523LS administered at 30 mg/kg IV infusion every 4 months

Primary endpoint 1:

- Local and systemic Solicited AE signs and symptoms, laboratory measures of safety, Unsolicited AEs, SAEs, AEs of special interest (AESI) and rates of discontinuation

Primary objectives 2:

- To determine whether multiple infusions of VRC07-523LS reach and maintain detectable levels in the mucosa
- To correlate levels of VRC07-523LS in serum and the mucosa

Primary endpoints 2:

- Levels of VRC07-523LS in genital and rectal secretions, as well as cervical, vaginal, and rectal tissues at the collection timepoints
- Levels of VRC07-523LS in serum out to Week 48, 16 weeks after the last product administration

5.2 Secondary objectives and endpoints

Secondary objective 1:

- To compare dose regimens of VRC07-523LS delivery for their ability to sustain mucosal mAb levels at serial timepoints post repeat administration

Secondary endpoint 1:

- Levels of VRC07-523LS in genital and rectal secretions and tissue at specified timepoints

Secondary objectives 2:

- To determine whether ADA can be detected in serum

Secondary endpoint 2:

- Serum concentration of ADA in each group measured at multiple timepoints from baseline through the final study visit

5.3 Exploratory objectives

Exploratory objective 1:

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

Exploratory objective 2:

To develop predictive mucosal population pharmacokinetic models of VRC07-523LS administered IV

Exploratory objective 3:

To conduct analyses related to furthering the understanding of HIV, monoclonal antibodies, immunology, vaccines, and clinical trial conduct

6 Statistical considerations

6.1 Accrual and sample size calculations

Recruitment will target accruing a total of 24 healthy, HIV-1–uninfected adult participants in two treatment groups, with 12 participants assigned to each group.

In Group 1, all study participants will receive three IV administrations of VRC07-523LS at the 10 mg/kg dose level. In Group 2, all study participants will receive three IV administrations of VRC07-523LS at the 30 mg/kg dose level.

In both groups, the three infusions will be administered every 16 weeks.

Participants will be randomly assigned to either one of the groups. Groups 1 and 2 will open to randomization at the same time.

In Groups 1 and 2, every study participant will be followed for 12 months (including 8 months of product administration plus 4 months of follow-up) from the day of first product administration.

To ensure balance in the trial of both sexes assigned at birth, the trial will enroll at least and approximately 50% of participants assigned female sex at birth. Randomization will be stratified by assigned sex at birth to ensure balance within each treatment group.

The times at which samples will be collected are listed in Table 9-1 and Table 9-2 for each mucosal site and the blood.

Since enrollment is concurrent with the first biopsy sample collection, all participants will provide some data regarding tolerability of mucosal sample collections. For analyses of VRC07-523LS levels in serum and mucosa and of data from ADA assays, it is possible that data may be missing for various reasons, such as participants terminating from the study early, problems in shipping specimens, or high assay background. Immunogenicity data from 17 phase 1 and 2 phase 2a HVTN vaccine trials, which began enrolling after June 2005 (data as of September 2014), indicate that 17% is a reasonable estimate for the rate of missing data. In HVTN 104 (phase 1 trial of VRC01), approximately 10-15% of drug concentration data were missing at the primary timepoints.

6.1.1 Sample size calculations for safety

The goal of the safety evaluation for this study is to identify safety concerns associated with product administration. All participants who receive at least one product administration will be included in this analysis. 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 each treatment group of size n = 12, there is

at least 90% chance of observing at least 1 event if the true rate of such an event is 17.5% or more; and there is at least 90% chance of observing no events if the true rate is 0.87% or less. For both groups combined (n = 24), there is at least 90% chance of observing at least 1 event if the true rate of such an event is 9.2% or more; and there is at least 90% chance of observing no events if the true rate is 0.43% or less. As a reference, in HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE.

Binomial probabilities of observing 0, 1 or more, and 2 or more events among arms of sizes 12 and 24 are presented in Table 6-1 for a range of possible true AE rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with VRC07-523LS.

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among groups of size 12 and 24 for a range of true event rates

True event rate (%)	arm size	0 events	1+ events	2+ events
1	12	0.89	0.11	0.01
	24	0.79	0.21	0.02
4	12	0.61	0.39	0.08
	24	0.23	0.77	0.42
10	12	0.28	0.72	0.34
	24	<0.02	>0.98	0.89
20	12	0.07	0.93	0.73
	24	<0.01	>0.99	>0.99
30	12	0.01	0.99	0.91
	24	<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 (CI) for the true rate of an AE based on the observed data. Table 6-2 shows the 2-sided 95% CIs for the probability of an event based on a particular observed rate. Calculations are done using the score test method (57). If none of the 12 participants in either Group 1 or Group 2 experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events in the population is 24.2%. If none of the 24 participants enrolled in Groups 1 and 2 experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events in the population is 13.8%.

Table 6-2 Two-sided 95% CIs based on observing a particular rate of safety endpoints for groups of size 12 and 24

Observed event rate (number of events / sample size)	95% CI (%)
0/12	[0 ; 24.2]
1/12	[1.5 ; 35.4]
2/12	[4.7 ; 44.8]
0/24	[0 ; 13.8]
1/24	[0.07 ; 20.2]
2/24	[2.3 ; 25.8]

6.1.2 Sample size calculations for serum and mucosal levels

One of the primary objectives of the study includes assessing the association between the levels of VRC07-523LS measured in serum and in mucosal secretions and tissues at various sites. Measurements will be collected in all 24 participants before the first infusion as well as at several timepoints following the first infusion. The primary statistical analysis will estimate associations between blood and mucosal levels within timepoints. These primary analyses will be conducted irrespective of dose (ie, data from Groups 1 and 2 will be combined) as well as within each treatment group. Additional analyses, secondary in nature, will evaluate association between the levels of VRC07-523LS in serum and in mucosal samples within each birth sex.

The power of the study to detect a significant association between the levels of VRC07-523LS (possibly transformed) measured in serum and in any given mucosa site is shown in Table 6-3 for several values of Pearson's linear correlation coefficient (r) and sample sizes (n). We anticipate that the primary correlation analysis will be based on samples of sizes n = 12 and n = 24. The secondary correlation analysis will be performed on samples of sizes that are expected to range between n = 5 and n = 15.

In an analysis combining all 24 participants from Groups 1 and 2, the study has more than 72% power to detect a significant association between measurements if the true value of the correlation coefficient is 0.5 or higher. If the true value of the correlation coefficient is 0.6 or higher, the power of the study is greater than or equal to 89.8%.

With 12 participants (eg, in any primary analysis assessing association within a particular treatment group, or in any secondary analysis within a particular birth sex combining both groups), the study has almost 77% power to detect a significant association between measurements if the true value of the correlation coefficient is 0.7 or higher.

With 6 participants (as in any secondary correlation analysis restricted to a specific sex assigned at birth and conducted within a particular treatment group, assuming balance in treatment groups), the study has more than 77% power to

detect a significant association between measurements if the true value of the correlation coefficient is 0.9 or higher.

Additional calculations are reported in the Table that account for 40% to 60% birth sex imbalance within groups. These calculations assumed a two-sided test at the 5% significance level. They were based on Cohen's method and used an arctanh transformation of the correlation coefficient defined by $Z' = arctanh(r) + r/(2(n-1))$ (58).

Table 6-3 Statistical power (in percent) to detect a significant association between serum and mucosal VRC07-523LS levels as a function of the sample size (n) for multiple true values of the correlation coefficient (r)

True correlation coefficient (r)	Sample size (n)						
	5	6	7	9	12	15	24
0.3	8.2	9.1	10.1	12.5	16.0	19.6	30.3
0.4	10.7	12.7	14.8	19.3	26.0	32.6	50.6
0.5	14.5	18.0	21.7	29.2	40.0	49.9	72.6
0.6	19.9	25.7	31.6	42.9	57.6	69.4	89.8
0.7	28.0	36.9	45.4	60.3	76.7	86.9	98.1
0.8	40.5	53.3	64.2	80.0	92.4	97.4	99.9
0.9	62.0	77.2	87.0	96.2	99.4	>99.9	>99.9

6.2 Randomization

Participants will enroll in the study at the first biopsy collection. Only participants who remain in the trial after the completion of the first biopsy visit will be randomized.

Accrual will continue until 24 participants have received first product administration.

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.

Groups 1 and 2 will be randomized simultaneously.

The randomization will be stratified by assigned sex at birth and done in blocks to ensure balance across both groups.

6.3 Blinding

Participants and site staff will be unblinded as to participant treatment group assignments. VRC07-523LS concentration and ADA assessments will be performed in a blinded fashion.

6.4 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment.

All analyses pertaining to safety and drug levels objectives of the study will be conducted with an intent-to-treat analysis that includes all randomized individuals per their randomization allocation. Additional analyses will be performed that account for the actual infusions and dose levels that each participant received.

Analyses will be performed using SAS and R. Other software may be used to perform additional exploratory analyses. Unless otherwise stated, all tests will be two-sided and performed at a 5% significant level. In particular, 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, VRC07-523LS concentrations, and laboratory measurements for primary, secondary, and exploratory 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 administration of VRC07-523LS will provide some safety data.

6.4.3.1 Solicited AEs

The number and percentage of participants experiencing solicited AEs, either signs or symptoms, will be tabulated by severity and treatment arm and the percentages displayed graphically by arm. For a given sign or symptom, each participant's solicited AEs will be counted once under the maximum severity for all administration 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 SAEs and Unsolicited AEs

Unsolicited 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 Unsolicited 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 Unsolicited 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 study product administration, and number of study product administrations received. A separate listing will do the same for AESI. A list of AESI to be reported for this protocol is provided in Appendix H.

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 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (see Section 9.10) will be tabulated by treatment arm for each postadministration 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.

6.4.3.5 Acceptability of study product or procedure

Acceptability of study product administration and infusion procedures will be tabulated by reason and treatment arm.

6.4.4 Analysis of antibody level endpoints

6.4.4.1 General approach

The second primary objectives of the study are to determine whether levels of VRC07-523LS in mucosa are detectable, and to correlate levels of VRC07-523LS in serum and mucosal sites.

In the primary statistical analysis, data from randomized participants will be used according to the initial randomization assignment regardless of how many administrations they received. Additional analyses may be performed, limited to participants who received all scheduled administrations per protocol. Assay results that are unreliable, from specimens collected outside of the visit window, or from HIV-infected participants postinfection may be excluded. Participants enrolled in this study will be recruited from a population at low risk of HIV infection. In the unlikely event of an HIV infection, since the exact date of infection is unknown, any assay data from blood draws or biopsy and secretion collections 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 will be excluded from the analysis. Biopsy and secretion collections will be discontinued in HIV-infected participants.

For continuous assay data (eg, levels of VRC07-523LS in serum and mucosa), graphical and tabular summaries of the distributions by treatment arm and timepoint will be made. Scatterplots and measures of association (eg, Spearman's rank and Pearson's linear correlation coefficients) and their 95% CIs will be constructed within each timepoint for every pair of serum and mucosa drug levels. Regression models may be used to describe association between two variables (eg, VRC07-523LS levels measured in a mucosal site versus VRC07-523LS levels in the serum), potentially adjusting for important confounders if needed. Independent samples (eg, VRC07-523LS levels measured in different treatment groups) may be compared using nonparametric tests (eg, Wilcoxon rank-sum or Mann-Whitney tests), whereas paired samples (eg, VRC07-523LS levels measured in mucosal secretions before and after the first drug administration) will be compared using Wilcoxon's signed rank test. If the normality assumption appears satisfied, two-sample *t*-tests with unequal variances, or parametric analysis of variance (ANOVA), or analysis of covariance (ANCOVA) adjusting for important covariates, may be used instead of the nonparametric tests when comparing independent groups. Likewise, the comparison of paired samples may be accomplished using one-sample *t*-tests. An appropriate data transformation (eg, logarithmic) may be applied prior to hypothesis testing to better satisfy analysis assumptions. For the analysis of correlation between two continuous assay variables over time, cross-correlation of the two variables with different time lags may also be calculated and visually displayed. Similar analyses stratifying by sex assigned at birth will be performed. Inference from these analyses will have limited power due to the small sample sizes of the groups.

The analysis of categorical variables derived from assay measurements (eg, whether VRC07-523LS levels are above a limit of detection or prebaseline levels) will be performed by tabulating the frequency of each category for each assay by group at each timepoint at which an assessment is performed. Frequencies will be presented with their corresponding 95% CI estimates calculated using the score test method (57).

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, 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 linear models for response rates may use a binomial error distribution and for continuous endpoints, a normal error distribution. All models will consider including as covariates all available baseline predictors of the missing outcomes.

Additional exploratory analyses will develop population PK models of VRC07-523LS in serum and mucosal sites, compare PK parameters across treatment groups, and assess whether any associations exist between PK parameters and participant's baseline covariates (eg, body weight, age, or sex at birth). Data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many administrations they received (MITT analysis). Serum concentration data that appear unreliable, or from HIV-infected participants postinfection will be excluded from the analysis. Serum concentration data from specimens collected outside of the visit window may be included in population PK analysis that account for the actual specimen collection time and the actual time of each product administration.

The proposed models will describe the PK of VRC07-523LS at the individual level using a compartmental approach. Based on a previous population PK analysis of the serum concentrations of VRC01, we anticipate that a two-compartmental model may suffice to characterize the kinetics of the serum concentrations of VRC07-523LS. In the event the modeling assumptions appear violated, we will consider other compartmental models. Serum concentrations from study participants will be described using a non-linear mixed effects model. Comparisons of PK parameters across treatment groups, doses, or routes of administration, will be performed using either likelihood ratio or Wald tests. Additional exploratory analyses will be performed to identify baseline covariates potentially associated with PK parameters of VRC07-523LS. Estimates of PK parameters, including area-under-the-curve (AUC), maximum concentration (Cmax), time to Cmax (Tmax), clearance (CL), volume of distribution (V), elimination rates and half-life, will be derived from these analyses. PK data on VRC07-523LS from other trials (eg, HVTN 127/HPTN 087) may be combined with PK data from HVTN 128 to avoid identifiability issues in these analyses.

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 analyses

During the course of the trial, analyses of safety data will be prepared approximately every 4 months during the main study for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 128 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-VRC07-523LS 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, product 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 information available at the time of enrollment, including results of screening 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 immunogenicity 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. **Access to a participating HVTN CRS** and willingness to be followed for the planned duration of the study

3. Ability and willingness to provide **informed consent**

4. **Assessment of understanding**: volunteer demonstrates understanding of this study and completes a questionnaire prior to first study product administration with verbal demonstration of understanding of all questionnaire items answered incorrectly

5. **Agrees not to enroll in another study** of an investigational research agent until completion of the last required protocol clinic visit

6. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

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

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

9. Assessed by the clinic staff as being at **"low risk" for HIV infection** and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit. See Appendix G for US Low risk guidelines.

Laboratory Inclusion Values

Hemogram/Complete blood count (CBC)

10. **Hemoglobin** ≥ 11.0 g/dL for volunteers who were assigned female sex at birth, ≥ 13.0 g/dL for volunteers who were assigned male sex at birth. For transgender participants who have been on hormone therapy for more than 6 consecutive months, determine hemoglobin eligibility based on the gender with which they identify (ie, a transgender female who has been on feminizing hormone therapy for more than 6 consecutive months should be assessed for eligibility using the hemoglobin parameters for persons assigned female sex at birth).

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

12. **WBC differential** either within institutional normal range or with site physician approval

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

Chemistry

14. **Chemistry panel**: **ALT** < 1.25 times the institutional upper limit of normal and **creatinine** ≤ institutional upper limits of normal.

Virology

15. **Negative HIV-1 and -2 blood test**: US volunteers must have a negative FDA-approved enzyme immunoassay (EIA) or chemiluminescent microparticle immunoassay (CMIA).

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

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

Urine

18. **Normal urine**:

    - Negative or trace urine protein

Reproductive Status

19. **Volunteers who were assigned female sex at birth**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test performed prior to biopsy collection and/or study product administration.

20. **Reproductive status**: A volunteer who was assigned female sex at birth must:

    - Agree to use effective contraception 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 128 PSRT
        - Successful vasectomy in any partner assigned male sex at birth (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);
        - Tubal ligation

    - Or be sexually abstinent until at least 4 months following the last study product administration.

21. **Volunteers who were assigned female sex at birth 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

22. **Volunteers 21 years of age and older who were assigned female sex at birth:** 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.

23. **Willing to have mucosal secretions and tissue biopsies collected at several timepoints**

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

7.2 Exclusion criteria

General

1. **Weight > 115 kg**

2. **Blood products** received within 120 days before first study product administration unless eligibility for earlier enrollment is determined by the HVTN 128 PSRT

3. **Investigational research agents** received within 30 days before first study product administration

4. **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 study

5. **Pregnant or breastfeeding**

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

7. **Previous receipt of humanized or human monoclonal antibodies (mAbs)**, whether licensed or investigational; the HVTN 128 PSRT will determine eligibility on a case-by-case basis.

8. **Previous receipt of monoclonal antibodies against HIV**

Immune System

9. **Immunosuppressive medications** received within 30 days before first infusion (Not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatitis; or [4] a single course of oral/parenteral prednisone or equivalent at doses $\leq$ 20 mg/day and length of therapy < 14 days)

10. **Serious adverse reactions to VRC07-523LS formulation components (sucrose, histidine, and sorbitol; see Section 8.2),** including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain.

11. **Immunoglobulin** received within 90 days before first infusion unless eligibility for earlier enrollment is determined by the HVTN 128 PSRT

12. **Autoimmune disease** (Not excluded from participation: Volunteer with mild, stable and uncomplicated autoimmune disease that does not require immunosuppressive medication and that, in the judgment of the site investigator, is likely not subject to exacerbation and likely not to complicate Solicited and Unsolicited AE assessments)

13. **Immunodeficiency**

Clinically significant medical conditions

14. **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 inability to establish venous access,
    - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period,
    - A condition or process (eg, chronic urticaria or recent infusion with evidence of residual inflammation) for which signs or symptoms could be confused with reactions to the study product, or
    - Any condition specifically listed among the exclusion criteria below.

15. **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, Solicited AEs, or a volunteer's ability to give informed consent

16. **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.

17. **Current anti-tuberculosis (TB) therapy**

18. **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.

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

20. **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.

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

22. **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)

23. **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.

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

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

Mucosal Specimen Collection

26. **A rectal condition (for rectal biopsies)**, 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.

27. **For those who were assigned female sex at birth (for 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 (eg, bacterial vaginosis).

28. **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.

29. **Hysterectomy or bilateral oophorectomy**

30. **Menopause**

31. **Current use of anticoagulants**

7.3 Participant departure from study product administration or withdrawal

This section concerns an individual participant's departure from the study product administration schedule. Pause rules for the trial are described in Section 11.3.

7.3.1 Delaying study product administration for a participant

Under certain circumstances, a participant's scheduled infusion will be delayed. Refer to the HVTN 128 Study Specific Procedures (SSP) for further guidance regarding which procedures to conduct in these instances. The factors to be considered in such a decision include but are not limited to the following:

- Within 7 days prior to any study product administration
  - Receipt of systemic glucocorticoids (eg, prednisone or other glucocorticoids) or other immunomodulators (other than nonsteroidal anti-inflammatory drugs [NSAIDs])

- Preinfusion abnormal vital signs or clinical symptoms that may mask assessment of study product reaction.

- Intercurrent illness that is not expected to resolve prior to the next scheduled study product administration which is assessed by the site principal investigator (PI) (or designee) to require delay or withdrawal from the study product administration schedule. The investigator may consult the HVTN 128 PSRT.

- Pregnancy: study product administration will be stopped while a participant is pregnant. If the participant is no longer pregnant (as defined by two consecutive negative tests) or breast-feeding and study product administration can be performed within an appropriate visit window, study product administration may resume with unanimous consent of the HVTN 128 PSRT.

Study product should not be administered outside the visit window period specified in the HVTN 128 SSP.

7.3.2 Participant departure from study product administration schedule

Every effort should be made to follow the study product administration schedule per the protocol. If a participant misses a study product administration and the visit window period for the study product administration has passed, that study product cannot be given. The participant should be asked to continue study visits. The participant should resume the study product administration schedule with the next study product administration unless there are circumstances that require further delay or permanent discontinuation of study product administration (see Sections 7.3.1 and 7.3.3).

7.3.3 Discontinuing study product administration for a participant

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

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of study product administration may be granted with the unanimous consent of the HVTN 128 PSRT)

- Clinically significant condition (ie, a condition that affects the immune system or for which continued study product administration and/or blood draws may pose additional risk), including but not limited to the following:
  - HIV infection
  - Any grade 4 local or systemic Solicited or Unsolicited AE that is subsequently considered to be related to study product;

  - Any grade 3 clinical AE (exception: fever and subjective local and systemic symptoms) that is subsequently considered to be related to study product (upon review, the HVTN 128 PSRT may allow continuation of study product administration if the participant has grade 3 erythema and/or induration)
  - Any grade 3 or 4 lab abnormality confirmed by a repeated value that is subsequently considered to be related to study product
  - SAE that is subsequently considered to be related to study product administration
  - Clinically significant hypersensitivity or mAb reaction including but not limited to type 1 hypersensitivity reaction, urticaria, or serum sickness associated with study product. Consultation with the HVTN 128 PSRT is required prior to subsequent infusion following any hypersensitivity reaction associated with study product

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

Participants discontinuing study product administration for reasons other than pregnancy and 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 (see HVTN 128 SSP).

Participants who become pregnant during the study should be encouraged to participate in follow-up visits (see Section 9.13). Participants diagnosed with HIV infection during the study should be encouraged to participate in follow-up visits (see Section 9.14).

7.3.4 Participant termination from the study

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

- Participant refuses further participation,
- Participant relocates and remote follow-up or transfer to another HVTN CRS is not possible,
- HVTN CRS determines that the participant is lost to follow-up,
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff), or

- Any condition where termination from the study is required by applicable regulations.

7.3.5 Delaying tissue biopsy and mucosal secretion collections for a participant

An individual participant's biopsy and mucosal secretion collections may be delayed in certain circumstances as described in Section 9.6. In addition to all mucosal collections, sexually transmitted infection (STI) and hormonal panel testing will be stopped while a participant is pregnant. If the participant is no longer pregnant (as defined by two consecutive negative tests) or breast-feeding and mucosal collections can be performed within an appropriate visit window, collections may resume with unanimous consent of the HVTN 128 PSRT.

Furthermore, if a participant receives a live attenuated vaccine other than influenza vaccine within 10 days prior to any tissue biopsy or mucosal secretion collection, mucosal sampling may be delayed and collections may resume with unanimous consent of the HVTN 128 PSRT.

7.3.6 Discontinuing tissue biopsies for a participant

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

- Increased 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 (see Appendix G)
- HIV infection
- Any medical condition that presents a contraindication for biopsies (eg, a condition requiring anticoagulants), in consultation with the HVTN 128 PSRT
- Investigator determination in consultation with the HVTN 128 PSRT and/or Protocol Team leadership
- The participant is no longer willing to provide biopsy specimens

8 Study product preparation and administration

HVTN 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 IB for further information about study products.

8.1 Study product regimen

The schedule of study product administration is shown in Section 3 and additional information is given below.

Group 1

Treatment 1 (T1): VRC07-523LS (VRC-HIVMAB075-00-AB) 10 mg/kg to be administered IV at weeks 0, 16, and 32.

Group 2

Treatment 2 (T2): VRC07-523LS (VRC-HIVMAB075-00-AB) 30 mg/kg to be administered IV at weeks 0, 16, and 32.

8.2 Study product formulation

VRC07-523LS will be supplied as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 mL ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow isotonic, sterile solution essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose and 2.5% sorbitol at pH 6.8.

Vials are intended for single use only and thus do not contain a preservative.

8.3 Study product storage

VRC07-523LS product label designates the long-term storage as -35°C to -15°C (-31°F to 5°F). Clinical site storage in a qualified, continuously monitored, temperature-controlled freezer with temperature excursions between -45°C to -10°C (-49°F to 14°F) is acceptable.

Following thaw, VRC07-523LS vials may be stored for up to 24 hours at controlled room temperature (maximum 27°C) and/or up to 2 weeks (14 days) at 2°C to 8°C. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, vials must be equilibrated at controlled room temperature (maximum 27°C) for a

minimum of 30 minutes and may be held at room temperature for up to 8 hours prior to product preparation.

8.4 Preparation of study products

Prior to preparation of the first dose, a new prescription will be sent to the pharmacy. The prescription MUST contain the participant's weight (in kg) based upon the participant's weight (in kg) at the most recent visit where weight was measured (this includes screening). If this information is NOT on the prescription, the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit.

Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight. A new prescription, which includes the new weight, must be written so that product can be prepared based on that weight change.

Pharmacists should keep in mind that the preparation instructions below are considered medium risk per USP 40 General Chapter / General Tests and Assays / Physical Tests and Determinations / <797> Pharmaceutical Compounding – Sterile Preparations, and should follow the requirements of their country, their institution, and their pharmacy regulatory authority regarding these procedures.

8.4.1 VRC07-523LS

VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing. When particles are observed, they may disappear after a few hours at room temperature or storage at 2°C to 8°C.

Ensure that only the required vials are present in the preparation unit during dilution and that medication labels are strictly segregated to avoid mix-ups.

The following instructions apply to thawing VRC07-523LS.

1. Thaw vial(s) for a minimum of 1 hour at controlled room temperature (maximum 27°C) after removing from the freezer.

2. Keep the material at room temperature during the entire preparation period until use, up to the maximum storage times described in Section 8.3.

3. 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 the particles dissolve within the maximum storage times

described in Section 8.3 for 2°C to 8°C storage, the vials may be used for product preparation. If the particles continue to be observed, do not use the vialed product for IV administration.

4. If the thawed material is not administered within 24 hours of thaw, follow the storage information provided in Section 8.3.

8.4.1.1 Intravenous infusion preparation instructions (T1 and T2):

1. Calculate the total milligrams of VRC07-523LS required based on the participant's weight (in kg) and the randomized treatment group of either 10 mg/kg or 30 mg/kg. Remove the total number of vials required from storage based on a 6 mL or 2 mL withdrawal volume containing 600 mg or 200 mg of VRC07-523LS, respectively.

2. Gently swirl thawed vials for 30 seconds to avoid 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 described above in Section 8.4.1.

4. Using aseptic technique, add the calculated volume of VRC07-523LS (total calculated milligrams of VRC07-523LS) to an appropriately sized IV container (bag/glass bottle) containing 100 mL of 0.9% Sodium Chloride Injection, USP that will also permit the addition of the required calculated volume of VRC07-523LS. Alternatively, if the pharmacist is using an IV container (bag/glass bottle) that cannot accommodate the full VRC07-523LS dose volume plus 100 mL of 0.9% Sodium Chloride Injection, USP, please refer to the Study Products Considerations section of the HVTN 128 SSP for further preparation instructions.

5. After product preparation in IV container (bag/glass bottle), the prepared VRC07-523LS may be stored at 2°C to 8°C for up to 24 hours or at room temperature (maximum 30°C) for a maximum of 8 hours total including the infusion time. Product may not be stored in direct sunlight. If stored at 2°C to 8°C, prepared product must be equilibrated at room temperature (maximum 30°C) for a minimum of 30 minutes prior to product administration.

6. Label the IV container (bag/glass bottle) as follows:

    - Participant identifier,

    - Participant weight (in kg)

    - Randomized dose of VRC07-523LS of either 10 mg/kg or 30 mg/kg and the total amount (mg) of VRC07-523LS added to the 0.9% Sodium Chloride Injection, USP

- Final volume of the IV container (bag/glass bottle)
- For IV administration
- Lot number

The prepared IV label should 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 stored at controlled room temperature (maximum 30°C)
- Product may not be stored in direct sunlight

Any unused portion of a VRC07-523LS 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 autoclaved in accordance with institutional or pharmacy policy.

8.5 Administration

8.5.1 VRC07-523LS Intravenously

For Groups T1 and T2

The IV container (bag/glass bottle) prepared by the pharmacy will include the weight that was used for preparation of the IV container (bag/glass bottle). The clinician responsible for administration will check the IV container (bag/glass bottle) label and confirm that the participant identifier is correct and that the weight on the IV container (bag/glass bottle) label is within 10% of the participant's current actual weight (refer to Section 8.4 for more information). The entire contents of the prepared investigational study product solution will typically be administered IV over about 15 to 60 minutes using a volumetric pump. The total time needed to administer the dose may be longer based on factors such as participant tolerance. The mL/hr infusion rate may vary based on the total volume needed to administer a full dose.

A 1.2 micron in-line filter infusion set must be used for IV product administration. In-line filters must comply with the specifications described in the HVTN 128 SSP. When the in-line filter is added to the tubing, prime the administration set with 0.9% Sodium Chloride Injection, USP. HVTN CRS staff may prime the administration set with VRC07-523LS only during a shortage of 0.9% Sodium Chloride Injection, USP. At the end of product administration, flush

the administration set with about 30 mL or appropriate volume of 0.9% Sodium Chloride Injection, USP.

8.6 Acquisition of study products

VRC-HIVMAB075-00-AB (VRC07-523LS) is provided by the VRC/NIAID.

Filter needles, in-line filter infusion sets and 0.9% Sodium Chloride for Injection, USP should be obtained by the site. Please refer to the study product considerations section of the HVTN 128 SSP for product specific reference numbers.

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 outlined in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

8.7 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.

8.8 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 study sponsor. The procedures are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

9 Clinical procedures

The schedule of clinical procedures is shown in Appendix F.

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 their IRB/EC and any applicable RE for human subjects protection review and approval.

Note: As defined in the DAIDS Protocol Registration Manual, an RE is "Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific ICFs [informed consent forms] prior to implementation at a site." HVTN 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 prevention clinical 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 main study is located in Appendix A. A separate sample consent form for other uses of specimens is located in Appendix B.

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 and Appendix B. The consent form(s) must be developed in accordance with requirements of the following:

- HVTN CRS's IRB/EC and any applicable REs,
- HVTN CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in 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 forms include instructions throughout the document for developing specific content.

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 clinical trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary.

Participants must verbalize understanding of all questions answered incorrectly. This process and the participant's understanding of the key concepts should be recorded in source documentation at the site.

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

9.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before enrollment biopsy collection on day –14. 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 (see Appendix G);
- 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
- Pap smear (only for volunteers 21 years or older who were assigned female sex at birth and who have not had a Pap smear performed within the last 3-5 years; for specific requirements see Section 7.1)
- Laboratory tests , including:
  - Screening HIV,
  - HBsAg,
  - Anti-HCV Abs,
  - CBC with differential ,

  - Chemistry panel (ALT, creatinine),
  - Syphilis,
  - Urine dipstick (urinalysis if indicated; see Section 9.9),
  - Urine or serum pregnancy test (volunteers who were assigned female sex at birth);
  - Chlamydia/gonorrhea (for all participants)
  - Trichomonas vaginalis (for participants providing cervicovaginal samples)
  - Bacterial vaginosis (for participants providing cervicovaginal samples)
  - Yeast (for participants providing cervicovaginal samples, only when clinically indicated)

- Administration of behavioral risk assessment questionnaire

- Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html)

- Counseling on HIV testing and risk reduction, performed in compliance with 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

- 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 assigned female sex at birth 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 (see Sections 7.1 and 7.2).

9.3 Enrollment visit

Enrollment is simultaneous with baseline biopsy collection on day –14. At the baseline biopsy visit, cervical, vaginal, and/or rectal biopsies and mucosal secretion specimens will be collected. These samples will serve as baseline controls and will help to assess both the participants' acceptability of the biopsy procedures and their fitness to continue with mucosal biopsy collections. Participants with conditions not amenable to biopsy sampling, not willing to continue in the trial after these baseline biopsies have been performed, or not able to provide mucosal secretions, will not be randomized. Participants not willing to continue in the trial after these baseline biopsies have been performed may be replaced.

Randomization will occur after the mucosal collection. The HVTN CRS requests the randomization assignment via a Web-based randomization system. In general, the time interval between randomization and infusion should not exceed 4 working days. However, circumstances may require a participant's infusion visit to be changed. This may exceed the 4-day randomization time limit. At the enrollment biopsy collection visit, 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 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 (see Section 9.2);
- Assessment of any new or unresolved Unsolicited AEs/intercurrent illnesses;
- Urine or serum pregnancy test (for participants who were assigned female sex at birth);
- Risk reduction counseling (see Section 9.7)
- For participants capable of becoming pregnant, pregnancy prevention assessment (see Sections 9.2 and 9.7)
- Social impact assessment
- Specimen collection (including mucosal and biopsy samples as described in Section 9.6);
- Laboratory tests (see Appendix E), including:

  - Blood hormone panel (estradiol and progesterone [assigned female sex at birth only])

- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate.

9.4 Infusion visits

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

- 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 any new or unresolved Unsolicited AEs/intercurrent illnesses (as described in Section 11.2.2);

- Assessment of concomitant medications (Section 9.2);

- Urine or serum pregnancy test (for participants who were assigned female sex at birth).

- Blood collection (see Appendix E)

- Mucosal secretion collection at infusions 2 and 3 only (see Section 9.6 and Appendix E).

Following completion of all procedures in the preceding list, and if results indicate that infusion may proceed, infusion is administered (see Sections 8.4 and 8.5).

Administration of all infusions during an infusion visit must be accomplished within 1 calendar day.

Immediately following infusion, the participant remains in the clinic for observation. See the HVTN 128 SSP for details regarding infusion visit protocols and subsequent infusion observation and Solicited AE assessment procedures (Section 9.10) that HVTN CRSs must follow. The HVTN CRS will make arrangements to be in contact with the participant during the Solicited AE period (as described in Section 9.10 and the HVTN 128 SSP).

The following procedures may be performed prior to, during, or following first infusion (see Appendix E and Appendix F):

- HIV infection assessment;

- Risk reduction counseling (see Section 9.7);
- For participants capable of becoming pregnant, pregnancy prevention assessment (see Sections 9.2 and 9.7);
- Administration of behavioral risk assessment questionnaire;
- Mucosal sampling acceptability questionnaire
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Administration of the social impact assessment questionnaire (types of impacts assessed involved personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);

For management of mAb reactions see the HVTN 128 SSP. The following procedures should be performed after a mAb reaction:

- mAb reaction clinical assessment
- mAb reaction blood collection.

9.5 Follow-up visits

Procedures will be performed at scheduled follow-up visits as specified in Appendix D and Appendix F:

- 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; or
- Complete physical examination (performed at last scheduled clinic visit), 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 ;
- Risk reduction counseling (as described in Section 9.7);
- Pregnancy prevention assessment (as described in 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 the participant has experienced any new social impacts as a result of 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);
- Assessment of new or continuing concomitant medications (as described in Section 9.2);
- Assessment of new or unresolved AEs/intercurrent illnesses or AESIs (as described in Section 11.2.2 and Appendix H;
- Mucosal sampling acceptability questionnaire
- Behavioral risk assessment questionnaire
- HIV diagnostic testing (see Section 9.7); 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;
- Specimen collection (including mucosal sampling as described in Section 9.6);
- Clinical laboratory tests, including:
  - CBC with differential,
  - Chemistry panel (see Section 9.2),
  - Blood hormone levels (estradiol and progesterone) for participants assigned female sex at birth only
  - Urine dipstick (urinalysis if appropriate; see Section 9.9),
  - Chlamydia/gonorrhea (for all participants)
  - Trichomonas vaginalis (for participants providing cervicovaginal samples when clinically indicated)
  - Bacterial vaginosis (for participants providing cervicovaginal samples, at indicated visits and when clinically indicated. See Appendix E)
  - Yeast (for participants providing cervicovaginal samples, when clinically indicated)
- Urine or serum pregnancy test (for participants who were assigned female sex at birth). Pregnancy test result required prior to biopsy collection.

CRS staff will contact study participants for a safety contact at Week 50 (see Appendix E and Appendix F).

9.6 Mucosal sampling

Mucosal secretion and biopsy samples will be collected at the timepoints indicated in Appendix D. All participants in this trial will have consented to mucosal specimen collections. Participants assigned male sex at birth will provide semen, rectal secretions, and rectal biopsies. Participants assigned female sex at birth will provide cervicovaginal and rectal secretions, as well as cervical, vaginal and rectal biopsies. Small (~2-4 mm) tissue biopsies are obtained from the vagina and ectocervix using a speculum and from the rectum by anoscopy by experienced clinicians. The product administration and biopsy collection schedules per mucosal compartment and visit are described in detail in Table 9-1, and also outlined in Appendix D; however, fewer samples may be taken based on the judgment of the performing clinician. The number of biopsies collected per mucosal compartment and visit is shown in Table 9-2. Following the first product administration, 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 HVTN 128 Sampling and product administration schedule

	D –14 W –2	D0 W0	D14 W2	D112 W16	D126 W18	D224 W32	D238 W34	D336 W48
Product Administration		X		X		X		
Blood collection	X	X	X	X*	X	X*	X	X
Rectal, cervicovaginal and seminal secretion collection	X		X	X*	X	X*	X	X
Cervical, rectal, and vaginal biopsy collection	X		X				X	X

* Specimen collections to be done prior to the infusion

Table 9-2 Biopsy and secretion specimen totals

	D –14 W –2	D14 W2	D112 W16	D126 W18	D224 W32	D238 W34	D336 W48	Total
Rectal biopsies	2	2				2	2	**8**
Cervical biopsies	2	2				2	2	**8**
Vaginal biopsies	2	2				2	2	**8**
Semen	1	1	1	1	1	1	1	**7**
Cervical secretions	2	2	2	2	2	2	2	**14**
Rectal secretions	1	1	1	1	1	1	1	**7**

- 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 assigned female sex at birth will be tested for trichomoniasis and bacterial vaginosis at indicated visits and may be tested for hyphae/budding yeast (when clinically indicated) as outlined in Appendix D. In addition to the predefined 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 STI) is present (as indicated below).

- If biopsy or secretion collections are delayed, they should be performed as soon as possible, within the visit window. Specimens should not be collected outside the visit windows specified in the HVTN 128 SSP. The participant should resume the collection schedule with the next collection unless there are circumstances that require further delay or permanent discontinuation of collections.

Rectal secretions and/or biopsy sampling

- For participants assigned female sex at birth and capable of becoming pregnant, a pregnancy test must be performed and be negative prior to any rectal mucosal sampling.

- 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 biopsy or 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 21 days from previous rectal biopsies.

- Participants must not have taken antithrombotic medications (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.

- Participant should not currently be taking anticoagulants. For participants with recent anticoagulant use, a CRS clinician must consult with the HVTN 128 PSRT for approval prior to collecting any tissue biopsies.

- Participants should not have receptive anal 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 an excessive 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 a participant who is capable of becoming pregnant, a pregnancy test must be performed and confirmed negative prior to biopsy sampling. For cervicovaginal secretion sampling, a pregnancy test must be done on the same day but can be performed prior to or after sampling.

- Cervicovaginal mucosal secretions cannot be collected during menstruation but should be performed as soon as possible, within the visit window.

- Cervicovaginal biopsies may be collected within the visit window during menses at the clinician's discretion.

- Cervicovaginal secretions or biopsy sampling will not be performed (or may be deferred to a later date within the visit window) if a participant has an active genital tract infection or lesion at the scheduled timepoint.

- Additional biopsy-specific criteria:
  - Biopsies will be collected a minimum of 21 days from previous cervical and vaginal biopsies.
  - Participants must not have taken antithrombotic medications (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.
  - Participant should not currently be taking anticoagulants. For participants with recent anticoagulant use, a CRS clinician must consult with the HVTN 128 PSRT for approval prior to collecting any tissue biopsies.
  - Participants should not have receptive 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 an excessive 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

- 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 genital tract infection 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 HIV-infected will be referred for medical treatment, counseling, and management of the HIV infection. With respect to enrolled participants who become HIV-infected, see Section 9.14.

It is theoretically possible that an anti-HIV mAb may suppress viral replication, which can reduce the ability to detect HIV, even if a person is 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

Tests of human plasma containing VRC07-523LS have been conducted using a variety of commercially available HIV test kits. At high plasma concentrations, reactive or indeterminate results have been observed on some test kits. See the HVTN 128 SSP for further detail. Thus, there is a possibility that receipt of the study product will cause a reactive result on some currently available HIV test kits, especially if testing occurs close to study product administration timepoints.

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.

9.8 Contraception status

Contraception status is assessed and documented at every scheduled clinic visit for a participant who was assigned female sex at birth 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 assigned female sex at birth 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.

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 menses or infection, document this issue in the participant's source documentation. For infection, provide appropriate treatment and/or referral. Following resolution, repeat the dipstick.

Follow-up urinalysis should be deferred if a participant is menstruating, but should be performed as soon as possible. If a follow-up dipstick is abnormal due to a participant's menstrual period, document in the comment section of the case report form (CRF) and repeat the dipstick once the participant is no longer menstruating. A micro-urinalysis is not required.

See relevant section of the Ab Manual of Operations (MOP) for further details.

9.10 Assessments of Solicited AEs

For all participants, baseline assessments are performed before and Solicited AE assessments are performed after each study product administration. All Solicited 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, except as noted in Section 11.2.2.

The Solicited AE assessment period is 3 full days following each study product administration per the assessment schedule shown in Table 9-3. Participants are instructed to record symptoms using a Participant Diary. The site staff and the participant will be in contact after the 3-day Solicited AE assessment period, or sooner if indicated. See the Ab MOP for further details. In general, a participant who self-reports any poststudy product administration reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved. Clinic staff will follow new or unresolved Solicited AEs present at day 3 to resolution.

Solicited AEs are reported using CRFs that correspond to the time of assessment in Table 9-3. Solicited AE assessments include assessments of systemic and local symptoms, and study product-related lesions. Events not listed on a CRF, or with an onset after the Solicited AE assessment period (day of study product administration and 3 full days after), or those meeting SAE/Unsolicited AEs requiring expedited reporting according to DAIDS criteria, are recorded on an AE Log.

Table 9-3 Schedule of Solicited AE assessments

Day	Time	Performed by
0[a]	Baseline: before infusion	HVTN CRS clinician
	Early: 25-60 minutes after infusion	HVTN CRS clinician
	Between early assessment and 11:59pm day 0	HVTN CRS clinician or participant
1-3[b]	Between 12:00am and 11:59pm on the respective day	HVTN CRS clinician or participant

[a] Day of infusion

[b] New or unresolved Solicited AEs present on day 3 are followed until resolution

9.10.1 Assessment of systemic and local symptoms

Systemic symptoms to be assessed as Solicited AEs in this trial include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, nausea, urticaria, non-exertional dyspnea, non-exertional tachycardia (assessed by HVTN CRS staff, not by the participant), generalized pruritus, facial flushing, and unexplained diaphoresis. Local symptoms include pain and/or tenderness at the infusion site. The daily maximum severity reached for each symptom during the assessment period is reported (see Ab MOP).

Body temperature is measured by oral or infrared thermometry. All temperatures must be measured by non-axillary thermometry. This includes temperatures taken in the clinic, as well as temperatures taken by participants during the Solicited AE period.

Temperature is 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

Typical infusion site reactions are erythema/redness and induration/swelling. The maximum diameter for all infusion/injection site reactions are recorded.

All infusion site reactions are monitored until resolution. Areas with diameters greater than 5 cm 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 128 SSP. For a visit not performed within the window period, a Missed Visit form is completed.

If a participant misses a scheduled visit, the HVTN CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. See the HVTN 128 SSP for more details.

If a missed visit required study product administration or if study product administration must be permanently discontinued, please refer to 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, Mucosal sampling acceptability questionnaire, safety contact, clinical laboratory tests (including urine dipstick, CBC with differential, and chemistry panel), pregnancy testing, social impact assessment, and HIV test. See relevant section of the Ab MOP for further details.

9.13 Pregnancy

If a participant becomes pregnant during the course of the study, no more infusions of study product will be given. During pregnancy, no more STI testing, hormonal panel testing, biopsy collections, and mucosal collections will be conducted. Remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. 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. Pregnancies and pregnancy outcomes will be reported.

If the participant is no longer pregnant (as defined by two consecutive negative tests) or breast-feeding and study product administration and mucosal collections

can be performed within an appropriate visit window, these may resume with unanimous consent of the HVTN 128 PSRT.

See relevant section of the Ab MOP for further details

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. In addition, no more STI testing, hormonal panel testing, biopsy collection, and mucosal secretion collections will be conducted. Participants will be encouraged to continue scheduled study visits 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 128 PSRT (eg, to avoid interference with participant initiation into HIV treatment). At postinfection follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected (see Appendix E and Appendix F).

See relevant section of the Ab MOP for further details.

10 Laboratory

10.1 HVTN CRS laboratory procedures

The HVTN 128 Site Lab Instructions and SSPs provide further guidelines for operational issues concerning the clinical and processing laboratories. These documents include 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 D. For tests performed locally, the local lab may assign appropriate tube types.

Of note, all assays described below are performed as research assays and are not approved for use in medical care. Results from these assays are not made available to participants or medical professionals to guide treatment decisions.

10.2 Total blood volume

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

10.3 VRC07-523LS concentrations

VRC07-523LS 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 immunoassay will be used to determine the concentration of VRC07-523LS. Ultra-sensitive bead-based analyses enable a broad dynamic range and higher sensitivity (eg, for the anti-idiotype mAb, 5C9, the lower limit of quantification is approximately 50 pg/mL). The operational sensitivity of the quantitative assays with respect to the various sample specimens will be determined for the clinical grade VRC07-523LS mAb used for this study. VRC07-523LS levels may be normalized relative to total protein and/or total IgG concentrations. Hemoglobin measurements may be used to perform quality control of mucosal secretions.

10.4 ADA detection assays

A tiered testing approach will be used to identify and characterize ADAs that may arise. Anti-VRC07-523LS antibody detection assays (screening, confirmatory,

and/or titration) will be performed on serum samples from study participants at indicated timepoints.

10.5 ADA functional assay

A functional ADA assay will be used to characterize any positive activity that is observed in the ADA detection assays. Functional activity will measure a reduction in VRC07-523LS neutralizing activity against a qualified virus in the TZM-bl assay.

10.6 Monoclonal antibody reaction assays

To investigate mAb reactions, serum samples collected after the onset of reaction may be tested to measure levels of certain markers (eg, tryptase, complement components (C3 and C4), and cytokines). ADA detection and functional assays, as described above, may be performed on serum samples taken prior to the study product administration associated with the reaction. Refer to the HVTN 128 SSP for more information.

10.7 Exploratory studies

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

10.8 Specimen storage and other use of 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 covered by the protocol or the informed consent form for the main study (see Appendix A).

This research may relate to HIV, vaccines, mAbs, the immune system, and other diseases. This could include 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 research on specimens will occur only after review and approval by the HVTN, the IRB/EC of the researcher requesting the specimens, and the HVTN CRS's IRBs/ECs/REs if required.

As part of consenting for the study, participants document their initial decision to allow or not allow their specimens to be used in other research, and they may

change their decision at any time. The participant's initial decision about other use of their specimens, and any later change to that decision, is recorded by their HVTN CRS in a Web-based tool that documents their current decisions for other use of their specimens. The HVTN will only allow other research to be done on specimens from participants who allow such use.

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

10.9 Biohazard containment

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

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

11 Safety monitoring and safety review

11.1 Safety monitoring and oversight

11.1.1 HVTN 128 PSRT

The HVTN 128 PSRT is composed of the following members:

- DAIDS medical officer representative
- Protocol chair and co-chair
- Protocol Team leader
- Core medical monitor
- Clinical safety specialist

The clinician members of the HVTN 128 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, clinical data manager, study product developer representative, clinical trial manager, and others may also be included in HVTN 128 PSRT meetings.

11.1.2 HVTN SMB

The SMB is a multidisciplinary group consisting of biostatisticians, clinicians, and experts in HIV prevention and drug research that, collectively, has experience in the conduct and monitoring of prevention and drug 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 Solicited AEs, Unsolicited AEs, laboratory safety data, and individual reports of AEs requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 128 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 clinical data;

- Providing reports of clinical data to appropriate groups such as the HVTN 128 PSRT and HVTN SMB (see Section 11.1.2);

11.1.4 HVTN Core roles and responsibilities in safety monitoring

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

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 128 PSRT AE review criteria (see Section 11.3);
- Notifying HVTN CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.3);
- Querying HVTN CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 128 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

Site staff must submit all safety forms (eg, Solicited AEs, Unsolicited AEs, urinalysis, local lab results, and concomitant medications) before the end of the next business day, excluding federal or bank holidays. 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. For the case of a longer site holiday closure, site staff must submit the data by the end of the 5th day (local time) after receiving the information even if this day is a holiday.

For example: If the site becomes aware of an AE on Thursday (Day 0), the site must submit the data by the end of the next business day, on Friday. If there is a longer site holiday closure, then this AE must be reported no later than the end of the fifth day, Monday (Day 4). If Monday is a holiday as well, all safety forms still need to be submitted by the end of Monday (Day 4).

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). See the Ab MOP and SSP for further detail regarding Solicited and Unsolicited AEs.

The study Unsolicited AE reporting period is from study enrollment of a trial participant to completion of the safety contact two weeks after the last biopsy collection at Week 50.

All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, 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 128 SSP);

- 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);

- Monoclonal antibody reactions (see HVTN 128 SSP)

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 (see Section 11.2.3) and (2), and (3) if the AE is listed as an AESI. A list of AESI to be reported in this protocol is provided in Appendix H.

Sites are expected to notify HVTN clinical safety staff 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/hvtn128). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, clinical safety staff will reply during working hours (their local time) to confirm that the email has been received and reviewed. If email service is not available, the HVTN CRS should notify clinical safety staff 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 AEs to DAIDS

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

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE (EAE) 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 CRMSsupport@niaid.nih.gov or from within the DAERS application itself.

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

The study product for which expedited reporting are required is:

- VRC-HIVMAB075-00-AB (VRC07-523LS)

While the participant is in the study, from enrollment to the end of trial participation for that participant, the SAE Reporting Category will be used.

After the end of trial participation for that participant, unless otherwise noted, only Suspected, Unexpected Serious Adverse Reactions (SUSARs) 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. All AESI will be considered “unexpected”, and, if deemed related to the study products, will be reported as SUSARs, if applicable.

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).

HVTN CRS Investigators of Record/designees will submit AE information and any other relevant safety information to their IRBs/ECs in accordance with IRB/EC requirements.

11.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and study product administration 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 128 PSRT AE review are summarized in Table 11-1. Study product administrations 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 128 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of study product administrations 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[b]
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 PSRT notification
SAE, related	Grade 3, 2, or 1	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause
AE[c], related	Grade 4 or 3	Email and submit forms immediately	Immediate PSRT notification and prompt 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/hvtn128).

[b] HVTN CSS or HVTN Core designee

[c] Does not include the following subjective Solicited AEs symptoms (infusion site pain and/or tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, non-exertional dyspnea, generalized pruritus, facial flushing, and unexplained diaphoresis).

For all safety pauses, HVTN Core notifies the HVTN 128 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 128 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of study product administration 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 product administrations. Based on the HVTN 128 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 128 PSRT notification or prompt HVTN 128 PSRT AE review is triggered, HVTN Core notifies the HVTN 128 PSRT as soon as possible

during working hours (HVTN Core local time)—or, if the information was received during off hours, by the morning of the next workday. If a prompt HVTN 128 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 HVTN CRS submit to its IRB/EC and any applicable RE protocol-related safety information (such as IND safety reports, notification of study-product holds due to the pause rules, unanticipated problems involving risks to participants or others, and notification of other unplanned safety pauses). HVTN CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 128 PSRT (see 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 128 PSRT AE review criteria.

11.4.2 Weekly review

During the study product administration phase of the trial, the HVTN 128 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. After the infusions and the following safety visit are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 128 PSRT. The HVTN CSS or HVTN Core designee reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the HVTN CRS clinic coordinator for verification.

11.5 Study termination

This study may be terminated early by the determination of the HVTN 128 PSRT, FDA, NIH, Office for Human Research Protections (OHRP), or study product developer(s). 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 trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Exploratory and ancillary studies and sub-studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS or HVTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the Ab MOP and HVTN 128 SSP.

12.1 Social impacts

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

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

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 HVTN 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 can contact the participant without IRB/EC approval if such communication is necessary to avoid imminent harm to the study participant. The HVTN CRS must 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 128 are described below.

Protocol history and modifications

Date: September 18, 2018

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.
  - Revised Guidelines for HIV Counseling, Testing, and Referral. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm
- 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 128 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 128 Study Specific Procedures (SSP). Accessible through the HVTN protocol-specific website.
- HVTN 128 Site Lab Instructions. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.

- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at http://www.iata.org/publications/dgr/Pages/index.aspx

- Lab assay algorithm (available upon request)

- International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6, 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 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/regulations-and-policy/regulations/45-cfr-46/index.html

See Section 16 for literature cited in the background and statistics sections of this protocol.

15 Acronyms and abbreviations

Ab	antibody
Ab MOP	Antibody Manual of Operations
ADA	antidrug antibodies
AE	adverse event
AESI	adverse event of special interest
AMP	antibody-mediated prevention
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
β-HCG	beta human chorionic gonadotropin
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 intervals
CRF	case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
EAE	expedited AE
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
Fred Hutch	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HVTN	HIV Vaccine Trials Network
IB	Investigator's Brochure
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHC	immunohistochemical

IND	Investigational New Drug
IoR	investigator of record
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
mAb	monoclonal antibody
MAR	missing at random
MOP	Manual of Operations
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NIH	US National Institutes of Health
OHRP	US Office for Human Research Protections
PAB	DAIDS Pharmaceutical Affairs Branch
PCR	polymerase chain reaction
PEP	postexposure prophylaxis
PI	Principal Investigator
PK	pharmacokinetic
PSRT	Protocol Safety Review Team
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SMB	Safety Monitoring Board
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	study specific procedures
STI	sexually transmitted infection
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UW-VSL	University of Washington Virology Specialty Laboratory
VRC	Vaccine Research Center (NIAID)

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Appendix A Sample informed consent form

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

Protocol number: HVTN 128

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 an antibody against HIV called VRC07-523LS. 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 these procedures below. Antibodies have been used successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 24 people will take part in this study at multiple sites. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

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

   - Is the study VRC07-523LS antibody safe to give to people?
   - Are people able to take the study antibody without becoming too uncomfortable?
   - How much of the antibody remains in the body as time passes?
   - How much of the antibody is found at the rectum, vagina, and penis?
   - How does the body's response to the antibody change depending on the amount and timing of the doses?

2. The antibody cannot give you HIV.

The study antibody is not made from actual HIV. It is impossible for the antibody to give you HIV. Also, it cannot cause you to give HIV to someone else. 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. This study antibody is experimental.

The formal name of the study antibody is VRC-HIVMAB075-00-AB. From here on, we will call it VRC07-523LS or the study antibody.

VRC07-523LS is an experimental product. That means we do not know if it will be safe to use in people, or if it will work to prevent HIV infection. VRC07-523LS is used only in research studies.

VRC07-523LS was developed by Vaccine Research Center at the US National Institutes of Health (NIH).

In laboratory and animal studies, the study antibody attached to and prevented infection by many kinds of HIV viruses from around the world. We do not know if it will act the same way when given to people. It will take many studies to learn if it will be useful for prevention of HIV or treatment of HIV. This study alone will not answer these questions.

Risks of the VRC07-523LS antibody:

This section lists the side effects we know about. There may be others that we don't yet know about, even serious ones. We will tell you if we learn about any new side effects.

The VRC07-523LS antibody has been tested for safety in animals. In animal studies, no safety problems were seen at doses 13 times higher than those used in this study.

As of July 2018, VRC07-523LS has been given by injection or by intravenous infusion (IV) in ongoing clinical trials at the NIH Clinical Center and in a multisite study. In the VRC 605 study, 25 participants have received the antibody by injection or by intravenous infusion (IV). In the HVTN 127/ HPTN 087 clinical trial, VRC07-523LS has been given by IV infusion to 24 people (8 people have received a low dose, 8 people have received a medium dose, and 8 people have received a high dose of the antibody). So far, the study antibody has not made people too uncomfortable or caused serious health problems. Two people who got the study antibody by infusion had chills, fever, nausea, body aches, rapid heartbeat, and headache. These feelings went away within 12 hours.

General risks of antibodies similar to VRC01:

As of July 2018, similar antibodies called VRC01 and VRC01LS have been given to people in 14 clinical studies in the United States, Peru, Brazil, Switzerland, Thailand, and in sub-Saharan Africa. In these studies, more than 3000 adults and 60 infants have gotten those study products.

In a previous study, one person who got VRC01 by injection had a rash. One person had a brief fainting spell several hours after getting VRC01 by IV infusion. To be safe, no more injections or infusions were given to these people. Some participants had mild body discomfort, muscle pain, or joint pain after getting a study antibody.

Many of these studies are still going on and we don't know which people got the study antibodies and which people got a placebo (a liquid with no antibody in it). After receiving the antibody or a placebo, many people said that they had mild pain, itching, or redness where the antibody or placebo was given to them. Of these people, some said they felt like they had the flu after getting the antibody, but that this feeling lasted a few hours at most.

VRC07-523LS and VRC01 may have other side effects that we do not know about yet.

General risks of antibodies:

Antibodies that are different from VRC07-523LS have been given to people for other illnesses. With those antibodies most side effects happen within the first 24 hours. Those antibodies have caused fever, stuffy nose, redness in the face, feeling weak or having low energy, chills, shaking, nausea, vomiting, pain, headache, dizziness, trouble breathing, high or low blood pressure, itchiness, rash, hives, diarrhea, racing heartbeat, chest pain, or swelling in the lip, tongue, throat or face.

Rarely, some antibodies have caused serious reactions that may be life-threatening. Two such serious reactions are:

- Anaphylaxis – a physical reaction that includes difficulty breathing, possibly leading to low blood oxygen, low blood pressure, hives or rash, and swelling in the mouth and face. This may occur soon after getting an antibody.

- Serum Sickness – a physical reaction that includes developing hives or a rash, fever, big lymph nodes, muscle and joint pains, chest discomfort and shortness of breath. This may occur several days to 3 weeks after getting an antibody.

Please tell us if you have ever experienced reactions similar to anaphylaxis or serum sickness, and the cause of the reactions if you remember.

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 VRC07-523LS or similar experimental antibodies.

Antibodies given to a person usually do not last in the body more than a few months. One of the goals of this study is to see how long VRC07-523LS will stay in the body. We don't know yet how long it will last, but it may be several months.

Joining the study

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

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

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

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

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

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

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

   - Checking your weight, temperature and blood pressure
   - Looking in your mouth and throat
   - Listening to your heart and lungs
   - Feeling your abdomen (stomach and liver)
   - Checking your veins to 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 assigned female sex at birth, we will test you for pregnancy. If you were assigned female sex at birth and are 21 years or older, you must have had a Pap smear within the last 3 to 5 years with the most recent result being normal. We will need to request a copy of your Pap smear result. 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 review the screening results with you. The screening results may show you are not eligible to join the study, even if you want to.

Site: 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 assigned female sex at birth and could become pregnant, you must agree to use birth control to join this study.**

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

You should not become pregnant during the study because we do not know how the study antibody could affect the developing baby. You must agree to use effective birth control at least 21 days prior to enrollment through the last required protocol 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 about 9 scheduled visits for just under one year.**

   We will ask you to come to the clinic about 14 days before the first infusion for tissue collections that will be compared with tissue collections taken after infusions. This is to see how much study product gets into the tissues. You'll come again within about 2 weeks after each infusion to draw your blood. We will do this so that we can look at how your body responds to the study product.

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 main study ends (for example, to tell you about the study results).

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

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

Site: Insert any costs to participants (eg, birth control costs for participants assigned female sex at birth who could become pregnant).

US sites: Include the following paragraph:

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 the study antibody by IV infusion.**

    There are 2 groups in this study. All people in both groups will get the study antibody by IV. The amount of antibody is different in each of the 2 groups.

    When getting 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. The first IV will take about one hour. Other IVs will probably take about 15 to 60 minutes each.

    Which group you are in is completely random, like flipping a coin. We have no say in which group you are assigned to. Neither will you. We can tell you which group you are assigned to.

11. **We will give you the study products on a schedule.**

    You will be in one of 2 groups. Both groups will get an IV infusion 3 times during the study, about every 4 months. You will get a different dose depending on which group you are in.

    Participants in Group 1 will get the lower dose. Participants in Group 2 will get the higher dose.

Group	Route	Dose	IV schedule		
			First infusion	4 months later	8 months later
1	IV	Lower	X	X	X
2	IV	Higher	X	X	X

You will have to wait in the clinic for about an hour after the first IV infusion and for about half an hour after the other IVs to see if there are any problems. Then for that night and for 3 more days, you will need to keep track of how you are feeling and if you have any symptoms. We will ask you the ways we can contact you. We will contact you about 3 days after each infusion to ask how you have been feeling. 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 the study products, 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 assigned female sex at birth
- 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.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 17 mL and 100 mL (2 tablespoons to 1/2 cup). Your body will make new blood to replace the blood we take out.

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

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

We will be looking for side effects. We will 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 assigned male sex at birth to provide semen as well as rectal fluids and tissue. We will ask all participants assigned female sex at birth to provide cervical and rectal fluids as well as cervical, rectal and vaginal tissues.

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

Semen collections (for persons assigned male sex at birth)

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** semen collection, we will ask you to follow these instructions:

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

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 to hold it open. The tube will go in about 6½ cm (about 2½ inches). A small balloon will be placed through the tube and into the rectum. The balloon will stay in for less than a minute. The balloon will be inflated to about half the size of a chicken egg 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 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 half a grain of rice from the lining of your rectum. These are called rectal biopsies. We will collect 2 biopsies at 4 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 5 to 10 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 5 days before we collect your rectal tissues, we will ask you not to take medicines that thin your blood or prevent blood clots. These medicines are called NSAIDS, and common examples include Ibuprofen (brand name Advil®) and Naprosyn (brand name Aleve®).

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 assigned female sex at birth)

We will collect cervical fluids by using either a soft sponge inserted into the opening of your cervix, or by using a disposable 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 a 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 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 assigned female sex at birth)

We will collect small samples of tissue about the size of half a grain of rice. We will collect up to 2 cervical and 2 vaginal biopsies at 4 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 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 10 minutes.

For the 5 days before we collect your cervical and vaginal tissues, we will ask you not to take medicines that thin your blood or prevent blood clots. These medicines are called NSAIDS, and common examples include Ibuprofen (brand name Advil®) and Naprosyn (brand name Aleve®).

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 to see how your immune system responds to the study antibody.

We will send your samples (without your name) to labs approved by the HVTN for this study, which are located in the United States. 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. The genetic testing will only involve some of your genes, not all of your genes (your genome). The researchers will study only 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.

These tests done on your samples are for research purposes, not to check your health. The labs will not give the results to you or this clinic because their tests are not approved for use in making health care decisions. These labs are only approved to do research tests.

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 use them in other studies and share them with other researchers.

These samples are called "extra samples". The HVTN will only allow your extra samples to be used in other studies if you agree to this. You will mark your decision at the end of this form. If you have any questions, please ask.

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

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

How long will the samples be stored? There is no limit on how long your extra samples will be stored. *[Site: Revise the previous sentence to 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 may 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 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 HVTN or other researchers? The samples and 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, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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 extra samples and information for other research
- Government agencies that fund or monitor the research using your extra samples and 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 and 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.

Site: 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,
- Any regulatory agency that reviews clinical trials,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- The NIH Vaccine Research Center and people who work for them,
- 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]

Site: 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.

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

18. **We may stop your IV 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 IV infusions.**

    This may happen if:

    - you do not follow instructions,
    - we think that staying in the study might harm you,
    - you get HIV,
    - 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 IV infusions and most sample collections if you become pregnant.**

    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 infusions and most sample collections, and we will 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. *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 giving blood:

In this study, we will do some routine medical procedures. These are taking blood from you. These procedures can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, blood clot, and (rarely) muscle damage or infection where the needle was inserted. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of 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 may be at increased risk for HIV or other sexually transmitted infection (STI) infection if you are exposed. Most people heal within 5 to 14 days, but some may take longer.

Personal problems/discrimination/testing HIV antibody positive:

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 have used several common HIV antibody tests to test samples of blood containing different amounts of the study antibody. Very high VRC07-523LS levels in the blood can cause positive or uncertain results on a few brands of HIV tests. Such high levels might exist for a short time after a person gets the study antibody. This means that for a few days after getting the antibody, certain HIV tests might say a person is infected with HIV when they really aren't.

For this reason, 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 VRC07-523LS 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:

It is unlikely, but the genetic tests done on your samples 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.

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 study antibody 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 study antibody might affect your HIV infection or how long it takes to develop AIDS.

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

Benefits

22. The study may not benefit you.

We do not know whether getting the study antibody 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 study antibody or a vaccine later becomes 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: Approval from HVTN Regulatory Affairs (at vtn.core.reg@hvtn.org) is needed for any change (other than those that the instructions specifically request or those previously approved by HVTN Regulatory Affairs) to the boxed text

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

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

If you become sick or injured in this study, there is a process to decide if it is related to the study antibody and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

The 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, independent experts will be asked to review the decision. You always have the right to use the court system if you are not satisfied.

Questions

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

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

This study has been reviewed and approved by a committee called the [name of local IRB/EC]. 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 or title and telephone number of person on IRB/EC] , at the committee.

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 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 keep track of your decision about how your samples and information can be used. You can change your mind after signing this form.

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

OR

☐ I agree to the option above *and* also to allow my extra samples and 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 entire discussion of this consent form.

Appendix B Approved birth control methods (for sample informed consent form)

Site: Any change to the following boxed text requires approval from HVTN Regulatory Affairs at vtn.core.reg@hvtn.org. You can remove the box around the text.

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

You must agree to use effective birth control 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 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 partner(s) assigned female sex at birth;
- You only have oral sex; or,
- You are sexually abstinent (no sex at all).

Remember: If you are having sex, male and female condoms are the only birth control methods that also provide protection against HIV and other sexually transmitted infections.

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

Appendix C Sample consent form for use of samples and information in other studies

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–uninfected adult participants

Protocol number: HVTN 128

Site: [Insert site name]

When samples are no longer needed for this study, the study sponsors want to use them in other studies and share them with other researchers. These samples are called "extra samples". The HVTN will only allow your extra samples to be used in other studies if you agree to this. You will mark your decision at the end of this 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: Revise the previous sentence to 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 may 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 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 HVTN or other researchers?

The samples and 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, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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

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, but your name and other personal information will not be included. 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. There may be other unknown risks.

10. What are the risks of genetic testing?

It is unlikely, but the genetic tests done on your samples 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.

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 extra samples and information for other research
- Government agencies that fund or monitor the research using your extra samples and 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 and 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 or title 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 or title and telephone number of the investigator or other study staff].

If you have questions about your rights as a research participant, contact
[name or title and telephone number of person on IRB/EC .

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. You can change your mind after signing this form.

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

OR

☐ I agree to the option above *and* also to allow my extra samples and 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 entire discussion of this consent form.

Appendix D Table of procedures (for sample informed consent form)

				Time after first IV visit						
Procedure	Screening visit	Enrollment visit –14 days	First infusion visit	2 weeks	4 months	4.5 months	8 months	8.5 months	48 weeks	50 weeks
Infusion			√		√		√			
Cervical fluid, rectal fluid, and semen samples		√		√	√	√	√	√	√	
Cervical, vaginal, and rectal tissue samples[1]		√		√				√	√	
Genital and rectal infection testing	√			√				√	√	
Medical history	√									
Complete physical	√								√	
Brief physical		√	√	√	√	√	√	√		
Urine test	√			√		√		√		
Blood drawn	√	√	√	√	√	√	√	√	√	
Pregnancy test	√	√	√	√	√	√	√	√	√	
HIV testing and pretest counseling	√				√		√		√	
Risk reduction counseling	√	√	√	√	√	√	√	√	√	
Interview/questionnaire	√	√	√	√	√	√	√	√	√	
Pap smear (if needed)	√									
Safety contact										√

[1]At each tissue sample visit, 2 samples will be taken from each location.

Appendix E Laboratory procedures

Procedure	Ship to[1, 2]	Assay location[1, 2]	Tube Type[4]	Tube size (vol. capacity)[4]	Visit: 1	2	3	4	5	6	7	8	9	10[20]	Total
					Day: Screening visit[3]	D-14	D0	D14	D112	D126	D224	D238	D336	D350	
					Week:	W-2	W0	W2	W16	W18	W32	W34	W48	W50	
							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**
HIV diagnostics[7]	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	10	—	10	—	20	—	**40**
Safety Labs															
CBC/ Diff / Platelets[19]	Local lab	Local lab	EDTA	5mL	5	—	—	5	—	5	—	5	—	—	**20**
Chemistry panel[5, 19]	Local lab	Local lab	SST	5mL	5	—	—	5	—	5	—	5	—	—	**20**
Hormone Levels															
Hormone panel[15]	Local lab	Local lab	SST	8.5mL	—	8.5	—	8.5	8.5	8.5	8.5	8.5	8.5	—	**59.5**
STI Serology															
Syphilis[8]	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	**5**
Drug Levels/Detection															
VRC07-523LS Ab levels	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	—	y	y	y	y	y	y	—	**0**
Anti-Drug Antibody (ADA)															
ADA detection assays	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	—	—	y	—	y	—	y	—	**0**
ADA functional neutralization	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	y	—	y	—	y	—	**0**
mAb Reaction Labs															
Tryptase / C3 and C4 complement / Cytokines	CSR	ARUP	SST	8.5mL	—	—	See footnote 17							—	**0**
ADA detection assays	CSR	HVTN Labs / VITL	SST	8.5mL	—	—	See footnote y							—	**0**
ADA functional neutralization	CSR	HVTN Labs	SST	8.5mL	—	—	See footnote y							—	**0**
STORAGE															
Serum storage	CSR	—	SST	8.5mL	—	76.5	17	51	51	51	51	51	51	—	**399.5**
Visit total					**25**	**95**	**17**	**79.5**	**69.5**	**69.5**	**69.5**	**79.5**	**89.5**	**0**	**594**
56-Day total[18]					**25**	**120**	**137**	**216.5**	**69.5**	**139**	**69.5**	**149**	**89.5**	**89.5**	
URINE COLLECTION															
Urine dipstick[14]	Local lab	Local lab			X	—	—	X	—	X	—	X	—	—	
Pregnancy Test[6]	Local lab	Local lab			X	X	X	X	X	X	X	X	X	—	
Chlamydia/Gonorrhea[9]	Local lab	Local lab			X	—	—	X	—	—	—	X	X	—	
RECTAL SWAB COLLECTION															
Chlamydia/Gonorrhea[9]	Local lab	Local lab			X	—	—	X	—	—	—	X	X	—	
CERVICAL/VAGINAL SWAB COLLECTION															
Chlamydia/Gonorrhea[9]	Local lab	Local lab			X	—	—	X	—	—	—	X	X	—	
Trichomonas vaginalis[10]	Local lab	Local lab			X	—	—	—	—	—	—	—	—	—	
Bacterial vaginosis[11]	Local lab	Local lab			X	—	—	X	—	—	—	X	X	—	
Yeast[12]	Local lab	Local lab			—	—	—	—	—	—	—	—	—	—	
MUCOSAL BIOPSY COLLECTION[13]															
Colorectal															**Total Biopsies**
VRC07-523LS Ab levels	CSR	HVTN Labs / VITL			—	2	—	2	—	—	—	2	2	—	
Visit total colorectal biopsies[16]					**0**	**2**	**0**	**2**	**0**	**0**	**0**	**2**	**2**	**0**	**8**
Cervical															
VRC07-523LS Ab levels	CSR	HVTN Labs / VITL			—	2	—	2	—	—	—	2	2	—	
Visit total cervical biopsies[16]					**0**	**2**	**0**	**2**	**0**	**0**	**0**	**2**	**2**	**0**	**8**
Vaginal															
VRC07-523LS Ab levels	CSR	HVTN Labs / VITL			—	2	—	2	—	—	—	2	2	—	
Visit total vaginal biopsies[16]					**0**	**2**	**0**	**2**	**0**	**0**	**0**	**2**	**2**	**0**	**8**
MUCOSAL SECRETION COLLECTION[13]															
Semen	CSR	HVTN Labs / VITL			—	X	—	X	X	X	X	X	X	—	
Cervicovaginal Secretions	CSR	HVTN Labs / VITL			—	X	—	X	X	X	X	X	X	—	
Rectal Secretions	CSR	HVTN Labs / VITL			—	X	—	X	X	X	X	X	X	—	

Footnotes

1 CSR = central specimen repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

2 HVTN Laboratories include: Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA), Dartmouth College (Hanover, New Hampshire, USA).

Non-HVTN laboratories: VITL = Vaccine Research Center - Immunology Testing Laboratory (Gaithersburg, Maryland, USA), ARUP Laboratories (Salt Lake City, Utah, USA).

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 For a participant who was born female (ie, assigned female sex at birth), pregnancy test must be performed on urine or blood specimens on the day of study product infusion with negative results received prior to infusion.

A pregnancy test must be performed and confirmed negative prior to biopsy sampling and rectal secretion sampling. For cervicovaginal secretion sampling, a pregnancy test must be done on the same day but can be performed prior to or after sampling.

7 At an early termination visit for a withdrawn or terminated participant (see Section 7.3.4), blood should be drawn for HIV diagnostic testing, as shown for visit 9 above. If the terminated participant is HIV-infected, do not collect blood for HIV diagnostic testing.

8 Syphilis testing will be done by serology.

9 In males, chlamydia/gonorrhea testing will be done with both rectal swabs and urine. In females, chlamydia/gonorrhea testing will be done with rectal swabs, and with urine or vaginal swabs. Testing will occur at indicated visits and when clinically indicated.

10 Trichomonas testing will be done with cervical/vaginal swabs or urine; testing will occur at screening and when clinically indicated.

11 Bacterial vaginosis testing will be done with cervical/vaginal swabs; testing will occur at the indicated visits and when clinically indicated.

12 Cervical/vaginal swabs will be collected from females for yeast only when clinically indicated.

13 Mucosal specimens will be collected once the participant has been found to have met mucosal specimen collection criteria specified in the HVTN 128 SSP.

14 And microscopy if needed.

15 Hormone panel is defined in Sections 9.3 (enrollment visits) and 9.5 (follow-up visits).

16 The visit total indicates the total number of colorectal, cervical, or vaginal biopsies collected per visit.

17 SST blood will be collected at specific timepoints after the onset of any mAb reaction. Refer to the HVTN 128 SSP for more information.

18 The 56-day total blood volume includes 10mL maximum blood loss per biopsy collection visit. It does not include up to 51mL SST blood collected for any mAb reaction; however, the 56-day limit is not exceeded at any visit by the possible collection of SST blood for a mAb reaction.

19 For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests (ie, CBC/Diff/Platelets and Chemistry Panel) will be collected.

20 For information concerning the visit 10 safety contact, see Section 11.2.2.

y = SST blood collected for serum storage will also cover specimen needs for VRC07-523LS drug levels/detection, and ADA detection and functional neutralization assays (including for any mAb reactions); no separate blood draw is needed.

Appendix F Procedures at HVTN CRS

	01[1]	02	03	04	05	06	07	08	09	10
Day:		D −14	D0	D14	D112	D126	D224	D238	D336	D350
Week:		W −2	W0	W2	W16	W18	W32	W34	W48	W50
Procedure	Scr	Enr	Inf 1		Inf 2		Inf 3			
Study procedures										
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	
Assessment of understanding	X	—	—	—	—	—	—	—	—	
Signed protocol consent	X	—	—	—	—	—	—	—	—	
Medical history	X	—	—	—	—	—	—	—	—	
Complete physical exam	X	—	—	—	—	—	—	—	X	
Confirm eligibility and obtain demographics	X	—	—	—	—	—	—	—	—	
Randomize	—	X	—	—	—	—	—	—	—	
Abbreviated physical exam	—	X	X	X	X	X	X	X	—	
Risk reduction counseling[16]	X	X	X	X	X	X	X	X	X	
Pregnancy prevention assessment[2]	X	X	X	X	X	X	X	X	X	
Behavioral risk assessment questionnaire[18]	X	—	—	—	X	—	X	—	X	
Social impact assessment	—	X	X	X	X	X	X	X	X	
Social impact assessment questionnaire	—	—	—	—	X	—	X	—	X	
Mucosal sampling acceptability questionnaire	—	—	X	—	—	X	—	—	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Intercurrent illness/Unsolicited AEs	—	X	X	X	X	X	X	X	X	
AESI	—	—	—	X	—	X	—	X	—	
HIV infection assessment[3, 18]	X	—	—	—	X	—	X	—	X	
Confirm HIV test results provided to participant[18]	—	X	—	—	—	X	—	X	—	X
Safety contact[15]										X
Study product administration[18]										
Infusion[4]	—	—	X	—	X	—	X	—	—	
Solicited AE assessment[5]	—	—	X	—	X	—	X	—	—	
Local lab assessments[17, 18]										
Screening HIV test	X	—	—	—	—	—	—	—	—	
Hepatitis B, Hepatitis C	X	—	—	—	—	—	—	—	—	
Syphilis	X									
Hormone panel	—	X	—	X	X	X	X	X	X	
Pap smear[6]	X	—	—	—	—	—	—	—	—	
Safety labs										
CBC, differential	X	—	—	X	—	X	—	X	—	
Chemistry panel[7]	X	—	—	X	—	X	—	X	—	
Urine collection										
Urine dipstick[8]	X	—	—	X	—	X	—	X	—	
Pregnancy (urine or serum HCG)[9]	X	X	X	X	X	X	X	X	X	
Chlamydia/Gonorrhea[10, 18,]	X	—	—	X	—	—	—	X	X	
Rectal swab collection										
Chlamydia/Gonorrhea[10, 18,]	X	—	—	X	—	—	—	X	X	
Cervical/vaginal swab collection [18]										
Chlamydia/Gonorrhea[10,]	X	—	—	X	—	—	—	X	X	
Trichomonas vaginalis [11]	X	—	—	—	—	—	—	—	—	
Bacterial vaginosis[12,]	X	—	—	X	—	—	—	X	X	
Yeast[13]	—	—	—	—	—	—	—	—	—	
Mucosal biopsy collection[14, 18]										
Colorectal biopsy	—	X	—	X	—	—	—	X	X	
Cervical biopsy	—	X	—	X	—	—	—	X	X	
Vaginal biopsy	—	X	—	X	—	—	—	X	X	
Mucosal secretion collection[14, 18]										
Semen	—	X	—	X	X	X	X	X	X	
Cervicovaginal secretions	—	X	—	X	X	X	X	X	X	
Rectal secretions	—	X	—	X	X	X	X	X	X	

[1] Screening may occur over the course of several contacts/visits up to and including day −14 prior to enrollment biopsy collection.

[2] Pregnancy prevention (contraception) assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant. For such participants, use of effective contraception is required from 21 days prior to the first study product administration until the last scheduled clinic visit.

[3] Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

[4] Specimen collection required at study product administration 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 with the 3 days prior to study product administration.

[5] Solicited AE assessments performed daily for at least 3 days following study product administration (see Section 9.10).

[6] Only for volunteers who were assigned female sex at birth, 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.

[7] Chemistry panels are defined in Section 9.2.

[8] And microscopy if needed.

[9] For a participant who was born female (ie, assigned female sex at birth), pregnancy test must be performed on urine or blood specimens on the day of study product infusion with negative results received prior to infusion. A pregnancy test must be performed and confirmed negative prior to biopsy sampling and rectal secretion sampling. For cervicovaginal secretion sampling, a pregnancy test must be done on the same day but can be performed prior to or after sampling.

[10] Chlamydia/Gonorrhea testing will be done with both rectal swabs and urine in males, and with urine and/or vaginal and rectal swabs in females; testing will occur at indicated visits and when clinically indicated.

[11] Trichomonas vaginalis testing will be done with cervical/vaginal swabs or urine; testing will occur at the indicated visits and when clinically indicated.

[12] Bacterial vaginosis testing will be done with cervical/vaginal swabs; testing will occur 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 HVTN 128 SSP. Mucosal biopsy collections must be at least 28 days from the previous biopsy collection.

[15] This contact can be done by email, text, or telephone call.

[16] Includes transmission risk reduction counseling for HIV-infected participants.

[17] For participants with confirmed diagnosis of HIV infection, only specimens required for scheduled “Safety labs” will be drawn (see Appendix E).

[18] Not applicable to HIV-infected participants.

Appendix G HVTN low risk guidelines for the US

The following are intended as guidelines for the investigator to help identify potential vaccine trial participants at "low risk" for HIV infection. These guidelines are based on behaviors within the last 6-12 months prior to enrollment; however, it may be appropriate to consider a person's behavior over a longer period of time than specified to assess the person's likelihood of maintaining low risk behavior. Some volunteers may not be appropriate for enrollment even if they meet these guidelines. These guidelines should be supplemented and interpreted with local epidemiologic information about HIV prevalence in your area and community networks. The investigator may review the risk level of any volunteer with the site PI and/or the Protocol Safety Review Team.

A volunteer may be appropriate for inclusion if he/she meets these guidelines:

1. Sexual behaviors

In the **last 12 months** did not:

- Have oral, vaginal or anal intercourse with an HIV-infected partner, or a partner who uses injection drugs
- Give or receive money, drugs, gifts or services in exchange for oral, vaginal or anal sex

AND

In the **last 6 months** has abstained from penile/anal or penile/vaginal intercourse, OR

In the **last 6 months**:

- Had 4 or fewer partners of the opposite birth sex for vaginal and/or anal intercourse, OR

Is an MSM (person born male with partner(s) born male) who, in the **last 12 months**:

- Had 2 or fewer MSM partners for anal intercourse and had no unprotected anal sex with MSM, OR
- Had unprotected anal intercourse with only 1 MSM partner, within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, the volunteer may then have had protected anal intercourse with 1 other MSM partner (total 2 or fewer partners in the last 12 months).

Is a transgender person, regardless of the point on the transition spectrum, having sex with men (born male) and/or other transgender persons, who in the **last 12 months**:

- Had 2 or fewer partners for anal or vaginal intercourse, and had no unprotected anal or vaginal sex, OR
- Had unprotected anal or vaginal intercourse sex with 1 partner only within a monogamous relationship lasting at least 12 months (during which neither partner had any other partners). If the monogamous relationship ended, may then have had protected anal or vaginal sex with 1 other partner (total 2 or fewer partners in the last 12 months).

AND

Uses or intends to use condoms in situations which may include penile/anal or penile/vaginal intercourse with new partners of unknown HIV status, occasional partners, partners outside a primary relationship, and/or partners known to have other partners.

2. Non-sexual behaviors

In the **last 12 months** did not:

- Inject drugs or other substances without a prescription
- Use cocaine, methamphetamine, or excessive alcohol, which in the investigator's judgment, rendered the participant at greater than low risk for acquiring HIV infection. The investigator's judgment should consider local epidemiologic information about HIV prevalence in the area and community networks.

A volunteer is NOT appropriate for inclusion if he/she:

Acquired an STI (i.e. new infection) in the last 12 months:

- Syphilis
- Gonorrhea
- Non-gonococcal urethritis
- Herpes Simplex Virus type 2 (HSV2)
- Chlamydia
- Pelvic inflammatory disease (PID)
- Trichomonas
- Mucopurulent cervicitis
- Epididymitis
- Proctitis
- Lymphogranuloma venereum
- Chancroid
- Hepatitis B

Appendix H Adverse events of special interest (AESI)

AEs of special interest (AESI) for this protocol include those listed below.

- Systemic lupus erythematosus (SLE)
- Systemic scleroderma (SSD) (Systemic sclerosis [SSc]), including diffuse systemic form and CREST syndrome
- Sjogren's syndrome (SS)
- Polymyositis/Dermatomyositis syndrome (PM/DM)
- Raynaud's syndrome
- Antiphospholipid antibody syndrome (APS)
- Idiopathic thrombocytopenic purpura (ITP)
- Crohn's disease
- Ulcerative colitis

Appendix I Protocol Signature Page

A phase 1 clinical trial to evaluate the safety and pharmacokinetics of VRC-HIVMAB075-00-AB (VRC07-523LS) in the sera and mucosae of healthy, HIV-1–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 (eg, US National Institutes of Health, Division of AIDS) and institutional policies

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Investigator of Record Name (print) Investigator of Record Signature Date

DAIDS Protocol Number: HVTN 128

DAIDS Protocol Version: Version 1.0

Protocol Date: September 18, 2018