



PROTOCOL

HVTN 130/HPTN 089

A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in healthy, HIV-uninfected adult participants

DAIDS DOCUMENT ID 38531

IND ### HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

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National Institutes of Health (NIH)
Department of Health and Human Services (DHHS)
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STUDY PRODUCTS PROVIDED BY

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1 Overview

Title

A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in healthy, HIV-uninfected adult participants

Primary objectives

Primary objective 1

To evaluate the safety and tolerability of PGT121 or PGDM1400 or 10-1074 when administered in sequence via intravenous infusion (IV) with VRC07-523LS (2-mAb combinations), and of PGDM1400, PGT121, and VRC07-523LS administered in sequence via IV (3-mAb combination)

Primary objective 2

To evaluate the serum concentrations and pharmacokinetics (PK) of PGT121, PGDM1400, 10-1074, and VRC07-523LS after a single 2-mAb administration and after each PGDM1400, PGT121, VRC07-523LS 3-mAb administration

Primary objective 3

To evaluate the individual mAb-specific serum neutralizing activity of PGT121, PGDM1400, 10-1074, and VRC07-523LS after a single 2-mAb administration and after each PGDM1400, PGT121, VRC07-523LS 3-mAb administration

Study products

- PGT121: a human monoclonal antibody (mAb) that targets the HIV-1 V3 glycan, centered on N332. It is provided by the Beth Israel Deaconess Medical Center and was manufactured under cGMP standards at Catalent Pharma Solutions (Madison, Wisconsin). Product is provided at 50 mg/mL as 10 mL glass vials with a 6 mL fill volume.
- PGDM1400: a human mAb that targets the HIV-1 V2 glycan, centered on N160. It is provided by the Beth Israel Deaconess Medical Center and was manufactured under cGMP standards at Catalent Pharma Solutions (Madison, Wisconsin). Product is provided at 50 mg/mL as 10 mL glass vials with a 6 mL fill volume.
- 10-1074: a human mAb that targets the HIV-1 V3 glycan, centered on N332. It is provided by NIAID/NIH and was manufactured under cGMP standards at

MassBio (Boston, Massachusetts). Product is provided at 20 mg/mL as 50 mL glass vials with a 30 mL fill volume.

- VRC-HIVMAB075-00-AB (VRC07-523LS): a human mAb that targets the HIV-1 CD4 binding site. It is provided by the VRC/NIAID/NIH and was manufactured under current Good Manufacturing Practice (cGMP) standards at the VRC Pilot Plant operated under contract by the Vaccine Clinical Materials Program, Leidos Biomedical Research, Inc. (Frederick, Maryland). Product is provided at 100 ± 10 mg/mL as 10 mL glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL glass vials with a 2.25 ± 0.1 mL fill volume.

Table 1-1 Schema

Study arm	N	Dose	Route	M0	M4
Group 1	6	20+20 mg/kg	IV	PGT121 VRC07-523LS	—
Group 2	6	20+20 mg/kg	IV	PGDM1400 VRC07-523LS	—
Group 3	6	20+20 mg/kg	IV	10-1074 VRC07-523LS	—
Group 4*	9	20+20+20 mg/kg	IV	PGDM1400 PGT121 VRC07-523LS	PGDM1400 PGT121 VRC07-523LS
Total	27				

IV = intravenous infusion. The mAbs are infused sequentially in the order shown.

* Opening enrollment in Group 4 follows review of safety data for all participants in Groups 1-3. Details described in Section [11.3.2](#).

Participants

27 healthy, HIV-1–uninfected volunteers aged 18 to 50 years

Multicenter design

Randomized by group in Groups 1-3; open label product administration in all groups

Duration per participant

12 months per participant in Groups 1-3; 16 months per participant in Group 4

Estimated total study duration

19 months (includes enrollment, planned safety holds, and follow-up)

Investigational New Drug (IND) sponsor

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

Study product providers

- PGT121: Beth Israel Deaconess Medical Center (Boston, MA, USA)
- PGDM1400: Beth Israel Deaconess Medical Center (Boston, MA, USA)
- 10-1074: National Institute of Allergy and Infectious Diseases (NIAID), NIH, DHHS (Bethesda, MD, USA)
- VRC07-523LS: Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, MD, USA)

Core operations

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

HPTN Leadership Operations Center (LOC), FHI360 (Durham, North Carolina, 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

- Fred Hutchinson Cancer Research Center (Seattle, Washington, USA)
- Duke University Medical Center (Durham, North Carolina, USA)
- Dartmouth College (Hanover, New Hampshire, USA)
- Vaccine Research Center – Immunology Testing Laboratory (Gaithersburg, Maryland, USA)

Study sites

HVTN and HPTN Clinical Research Sites (CRSs) in the United States to be specified in the Site Announcement Memo

Safety monitoring

HVTN 130/HPTN 089 Protocol Safety Review Team (PSRT); HVTN Safety Monitoring Board (SMB)

1.1 Protocol Team

Protocol leadership

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2 Ethical considerations

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

- Network trials are designed and conducted to enhance the knowledge base necessary to find new methods for 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.
- Network 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.
- Network scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. Community Advisory Boards (CAB) are required by DAIDS and supported at all Network research sites to ensure community input.
- Network clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV-infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
- The Networks require that all international Network sites lacking national plans for providing antiretroviral therapy (ART) develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the Networks. 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 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 Networks provide training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have

their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.

- Prior to implementation, Network trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.
- Network trials are reviewed by local and national regulatory bodies and are conducted in compliance with all applicable national and local regulations.
- The Networks design their research to minimize risk and maximize benefit to both study participants and their local communities. For example, Network protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. Network protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.
- Network research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in Network trials are able to conduct other critical research in their local research settings.
- The Networks recognize the importance of institutional review and value 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.

3 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 Network Investigator welcomes IRB/EC/RE questions or concerns regarding these research requirements.

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

3.1 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 at birth); and (f) providing safety monitoring.

3.2 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.

3.3 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.

3.4 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 Networks as part of its entering the Network. The Networks require a signed consent document for documentation, in addition to chart notes or a consent checklist.

3.5 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 11). Safety is monitored daily by HVTN clinical staff and routinely by the HVTN 130/HPTN 089 PSRT. In addition, the HVTN SMB periodically reviews study data.

3.6 Protect privacy/confidentiality

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

Privacy refers to an individual's right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term "privacy" concerns research participants or potential research participants as individuals whereas the

term “confidentiality” is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see [Appendix A](#) and [Appendix B](#)). The privacy of participants is protected by assigning unique identifiers in place of the participant’s name on study data and specimens. In the United States, research participants in Network protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data and Specimens with the Networks. 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.

4 Background

Broadly neutralizing HIV-1 antibodies (bnAbs) occur in many HIV-1 infected individuals, usually after several years of infection (4). However, it remains a challenge to elicit them by vaccination because broad and potent HIV-1 neutralization often requires unusual antibody characteristics, such as long hypervariable loops, autoreactivity with host antigens, interaction with glycans, and high levels of somatic mutation in the variable domains, which are important to facilitate binding to the highly glycosylated HIV-1 envelope protein (5-7). Thus, there is an interest in passive immunization with monoclonal antibodies (mAbs) modeled on these naturally-occurring bnAbs to prevent, treat, and potentially cure HIV-1 infection, as well as an interest in studying bnAbs to inform and expedite the development of HIV vaccines that may elicit such antibodies.

Over the past decade, dozens of bnAbs have been identified and their HIV-1 target sites and mechanisms of neutralization have been elucidated (5, 8-14). These efforts have informed the design of recombinant protein immunogens that can potentially elicit broadly neutralizing antibodies (12, 15-19) and they have set the stage for evaluation of these antibodies' potential to contribute to HIV-1 prevention (ie, passive immunization or antibody-mediated prevention), treatment, and possibly cure (20-24). Passive infusion studies in non-human primates (NHP) demonstrated that bnAbs were effective in protection against mucosal simian-human immunodeficiency virus (SHIV) challenge (25-32). Results from early phase human clinical trials using different classes of bnAbs, such as those targeting the CD4 binding site (VRC01 and 3BNC117) and the V3 loop (10-1074 and PGT121), have been encouraging, demonstrating the potential for and challenges of developing anti-HIV-1 bnAbs as preventive and therapeutic agents (33-38).

Passive immunization for prevention is a long-standing strategy that has been employed for more than 100 years against diverse disease targets and is still used for hepatitis A and B prophylaxis, for prevention of transplant-associated cytomegalovirus (CMV) infection, and as postexposure prophylaxis for rabies, measles, varicella zoster, and other infectious diseases (39-41). In 2016, VRC01 advanced to the first prevention efficacy trials in HIV-uninfected individuals. In addition to assessing safety and PK data, these efficacy trials (HVTN 704/HPTN 085 [NCT02716675] and HVTN 703/HPTN 081 [NCT02568215]) include assessment of non-neutralizing antiviral activity (ie, Fc effector functions), sieve analysis, and correlates analyses (42). These are important proof-of-concept trials to determine whether antibodies that neutralize HIV-1 in vitro and protect nonhuman primates from experimental SHIV challenge will protect against the acquisition of HIV infection in humans. They also aim to determine the protective titer as a critical parameter in designing future clinical trials.

In HIV-1-infected patients, reductions in viral load have been observed after one infusion of a single bnAb, thus demonstrating the biological activity of HIV

bnAbs (35, 36, 43). A modest delay of viral rebound was also observed when bnAbs were infused after antiretroviral drugs were discontinued in previously suppressed HIV-infected individuals (44, 45). Improved neutralizing antibody activity in treated patients was also observed. However, viral resistant strains emerged rather quickly in most patients (34, 36, 43, 44, 46). Notably, recent tests of bnAb combinations have produced more durable viral suppression following analytical treatment interruption (38).

4.1 Rationale for trial concept

The development of mAbs for the potential prevention and treatment of HIV is evolving rapidly. Multiple broadly neutralizing mAbs have been developed, each of which targets 1 of 5 known sites on the HIV-1 Env protein (see [Figure 4-1](#)). These mAbs display a broad range of neutralization potency and breadth and some of the more promising have been engineered for improved neutralization, manufacturability, stability, and serum half-life. Additional improvements continue to be made, including the construction of bi- and tri-specific mAbs. While relatively few HIV neutralizing mAbs are currently available for clinical evaluation, those that are available include some of the most broad and potent mAbs identified to date. Thus, the available products, though limited, provide opportunities to address important scientific questions through clinical evaluation.

Since all bnAbs are limited in their breadth and potency, it is widely believed that some combination of complementary bnAbs will be required for effective HIV prophylaxis, a proposition supported by NHP challenge studies showing that a combination of 2 bnAbs fully protected macaques against a mixed SHIV challenge when neither mAb administered alone was able to do so (47) (see [Section 4.5.2.2](#)).

The bnAbs in this trial were selected for their neutralization potency, breadth of HIV-1 strain coverage, and their complementarity. As shown in [Figure 4-1](#), PGT121, PGDM1400, 10-1074, and VRC07-523LS target different sites on the HIV trimer. They also differ in the potency with which they neutralize different HIV-1 virus strains and in the range and number of different strains that they neutralize, with desirable complementarity ([Figure 4-2](#)). When tested in vitro against multiclade panels of HIV-1 pseudoviruses, PGT121 and PGDM1400 display limited coverage of viral strains (ie, breadth), but they also display outstanding potency, having among the lowest median IC₅₀ and IC₈₀ titers among all bnAbs identified to date (48) (see [Sections 4.2.1](#) and [4.2.2](#)). VRC07-523LS, a highly engineered derivative of the bnAb VRC01, displays somewhat lower potency than PGT121 or PGDM1400 but has outstanding breadth and an improved PK profile (see [Section 4.2.4](#)). The mAb 10-1074 targets the same V3 supersite as PGT121 and exhibits a similar neutralization profile, thereby affording alternative choices for this site based on potential differences that might arise in mAb manufacturability, safety, tolerability and PK.

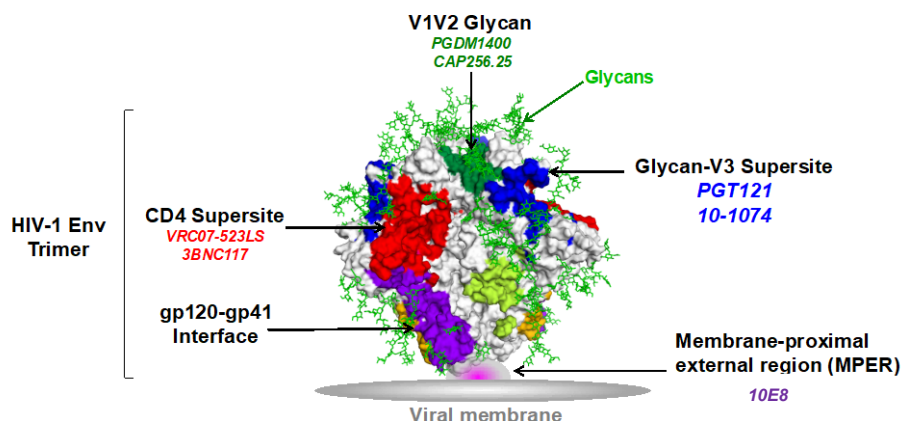


Figure 4-1: Antibody targets on the HIV-1 trimer (image by Stewart-Jones, Doria-Rose, Stuckey; adapted from (49, 50))

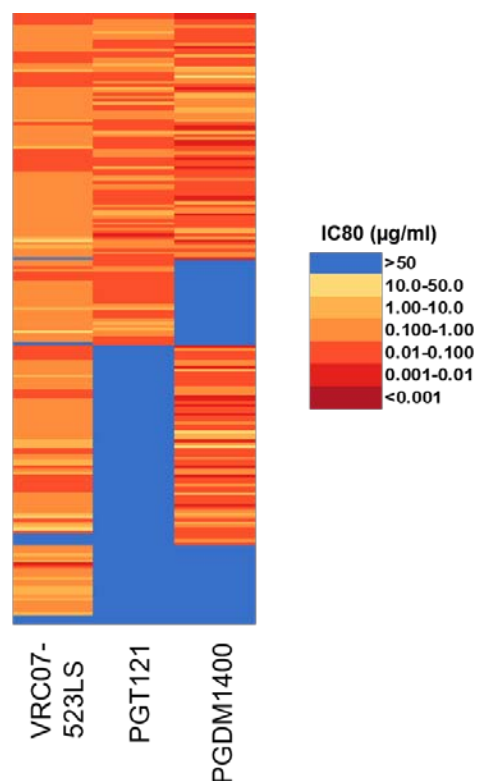


Figure 4-2 In vitro neutralization heat map of VRC07-523LS, PGT121, and PGDM1400 measured on multiclade pseudovirus panel (n = 208)

In vitro models suggest that administering these mAbs in combination will produce more potent and broader neutralization than administering any one mAb by itself (compare solid and dotted lines in [Figure 4-3](#)). Comparison of the solid lines in [Figure 4-3](#) suggests that administering all 3 mAbs in combination may produce neutralization superior to any of 2 of the mAbs in combination.

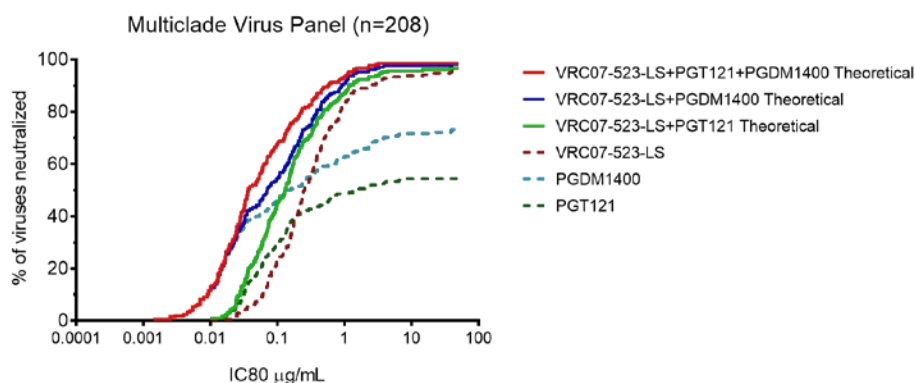


Figure 4-3 Predicted breadth and potency curves for PGT121, PGDM1400, VRC07-523LS and combinations of these mAbs against a panel of multiclade HIV isolates

Indeed, modeling by Korber, Wagh, and colleagues based on in vitro data suggests that this may be among the best performing combination of mAbs currently available (51-53). [Figure 4-4](#) depicts a comparison of the in vitro neutralization performance of VRC07-523LS + PGDM1400 + PGT121 against other combinations of 3 mAbs for protection against HIV-1 infection. Shown are predicted IC_{80} magnitude-breadth plots for VRC01-PGDM1400-10E8v4 Trispecific, a wide variety of 3-bnAb combinations, and VRC07-523LS + 10E8v4-V5R-100cF, which was identified as the best 2-bnAb combination. The figure on the far left shows data for the full global panel ($n = 208$), and the next figures show predicted performance against specific subtypes from this panel. The triple combination of VRC07-523LS + PGT121 + PGDM1400 is among the top performing combinations (among 56 triple bnAb combinations evaluated) when one considers all subtypes combined, subtype B alone, and subtype C alone, but is less effective against subtype AE, mainly because of poor coverage of this latter subtype by PGT121. The coverage of IC_{80} neutralization at 10 mcg/ml (3.3 mcg/ml each bnAb) was 98.6% for the full virus panel, with 95.6-98.3% across subtypes. Importantly, the dual and triple mAb combinations to be evaluated here are far superior to VRC01 in vitro ([Figure 4-4](#)).

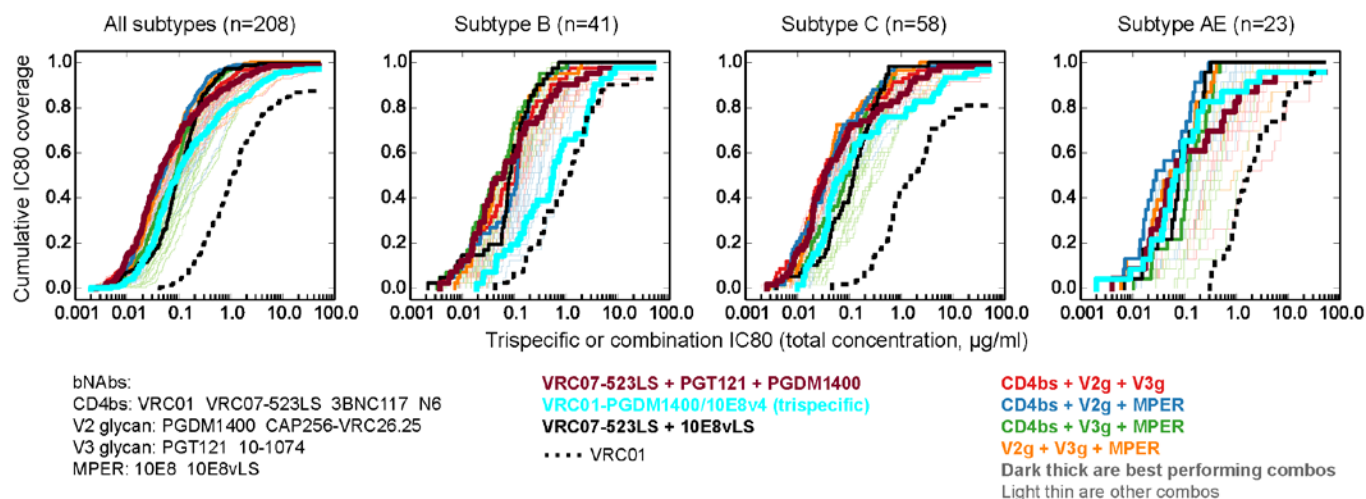


Figure 4-4 Comparison of the in vitro performance of VRC07-523LS + PGDM1400 + PGT121 against a Trispecific bnAb and combinations of 3 bnAbs under clinical development for passive protection against acquisition of HIV-1 infection

Based on preliminary PK data, VRC07-523LS has a longer half-life than PGT121 (Figure 4-5); likewise, PGDM1400, similarly lacking the “LS” modification, is also expected to have a shorter half-life than VRC07-523LS. However, it is important to note that PGT121 and PGDM1400 are more potent against the HIV strains they neutralize than is VRC07-523LS, potentially mitigating, at least in part, their shorter half-lives.

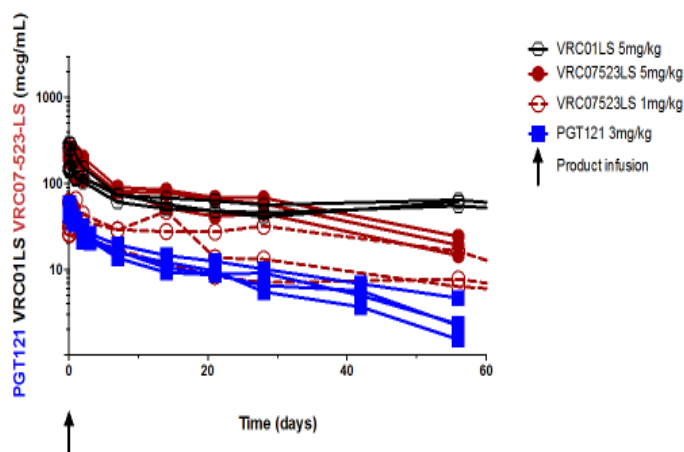


Figure 4-5: Serum concentrations (mcg/mL) for VRC01LS at 5 mg/kg and VRC07-523LS at either 1 mg/kg or 5 mg/kg compared to PGT121 at 3 mg/kg following a single IV infusion in humans.

Like PGT121, 10-1074 targets the potential N-linked glycosylation site at Asn332gp120 and the C-terminal base of the Env variable region 3 (V3) loop. Also like PGT121, 10-1074 exhibits potent neutralizing activity, including broad reactivity against transmitted founder viruses (see Section 4.2.3) (36).

Early product development assessment of the mAbs proposed for combination in this trial has revealed an attractive product profile, including safety and tolerability in early human trials (see Section 4.6). Thus, it is scientifically sound to evaluate VRC07-523LS, PGT121, 10-1074, and PGDM1400 together in a phase 1 human clinical trial to assess safety (including anti-drug antibodies [ADA]), PK, and functional activity, and to establish an experimental platform in preparation for further clinical testing of mAb combinations. In addition, testing mAbs (10-1074, PGT121) that target the same epitope will provide early information about the safety, tolerability, PK, and antiviral activity of each mAb in combination with VRC07-523LS. This information will expand the options for optimizing future combination products and is similar to the approach taken to development of combination therapies for HIV. Because of limited availability of 10-1074, 10-1074 and VRC07-523LS will only be evaluated in combination, while a regimen comprising PGDM1400, PGT121, and VRC07-523LS, a 3-mAb combination, will be evaluated in Group 4. The combination of these 3 mAbs with distinct epitope specificities will provide valuable experience assessing the potential additive, synergistic, or antagonistic properties of 3 bnAbs administered sequentially at the same study visit.

The overarching aims guiding this study are to characterize the safety, tolerability, and PK of mAbs when administered in combination; and to describe whether, in humans, there is an increase in neutralization potential with combination mAbs and whether neutralization varies by antibody and site of binding. Given NHP data, in vitro modeling data, and experience from the antiretroviral field (51, 52), it is likely that a combination of multiple antibodies targeting different key epitopes on the viral envelope may be necessary for efficacy and thus testing different mAb combinations is an important first step. Even though newer, LS formulations of mAbs such as PGDM1400, PGT121, and 10-1074 will be tested in future studies, testing whether neutralization breadth and potency can be augmented with multiple mAbs is an important first step. Furthermore, these data will start generating information about interchangeability of mAbs targeting the V3-N332 glycan with respect to neutralization, ADA, and PK.

Taken together, data collected in this protocol will contribute significantly to future analyses and to the design of future studies seeking to optimize mAb combinations for HIV-1 prevention.

4.2 Study products

4.2.1 PGT121

PGT121 is a broadly neutralizing mAb that was identified from African donor 17 of the IAVI Protocol G cohort. It is a human mAb that targets the V3 glycan-dependent epitope region of the HIV-1 virus. This epitope on the gp120 outer domain includes both protein and glycans and is centered on the conserved residue N332 (54-56). Using a 162-pseudovirus panel, representative of all major

HIV-1 circulating clades, PGT121 had a 10-fold higher median neutralizing potency than mAbs PG9, VRC01, or PGV04 and a 100-fold higher potency than 2G12, b12, or 4E10 (48). While PGT121 neutralized a smaller percentage of the panel of pseudoviruses than VRC01 at an $IC_{50} < 50$ mcg/mL (63% for PGT121 vs. 93% for VRC01), it exhibited high potency against the sensitive strains, with neutralization of 44% of the 162-virus panel at an $IC_{50} < 0.1$ mcg/mL. This percentage is almost twice the neutralization under the same conditions as PG9, VRC01, PGV04 and 20–40 times more neutralizing than 2G12, b12, and 4E10, all of which have been investigated previously in passive protection studies (48, 57, 58).

4.2.2 PGDM1400

PGDM1400 is a broadly neutralizing mAb that was recently identified from African donor 84 of the IAVI Protocol G cohort. PGDM1400 is a human mAb that interacts with glycans in the region of N160 on the V2 loop of gp120 Env (57). The PGDM1400 antibody is highly quaternary-structure dependent and was discovered by using a recombinant HIV envelope trimer, BG505 SOSIP.664 gp140, as an affinity reagent (57). It is exceptionally broad and potent, with 83% global coverage at a median IC_{50} of 0.003 mcg/mL, and is, therefore, 10 to 100-fold more potent than the previous best in class CD4bs antibodies VRC01, VRC07, and 3BNC117 (47, 48, 57, 58).

PGDM1400 and PGT121 are complementary in their coverage of global viral isolates. In combination they neutralize 98-99% of global HIV-1 viruses tested in a 106-pseudovirus panel and have unparalleled potency with a median IC_{50} of 0.007 mcg/mL (57).

4.2.3 10-1074

10-1074 is a human mAb that was isolated at the Rockefeller University from an African donor who was infected with a clade A HIV-1 virus and who displayed high titer serum neutralization activity (59). Like PGT121-123, 10-1074 recognizes an epitope on the gp120 V3 outer domain that includes both protein and glycans, centered on the conserved residue N332 (60, 61).

When tested against large panels of HIV-1 pseudoviruses in TZM.bl neutralization assays in vitro, 10-1074 neutralizes 65% of 306 strains comprising 13 subtypes and 88.5% of 26 clade B strains at an average IC_{80} of 0.18 mcg/mL and 0.13 mcg/mL, respectively (36) (Figure 4-6). When tested against primary HIV-1 isolates from 179 persons with HIV-1 infection (77 off and 102 on ART) living in the US and Germany, 77.7% of cultures were neutralized, with a mean IC_{80} of 0.67 mcg/mL (36).

Subtype	Tested strains	Mean _{IC₈₀} *	Neutralized (%)**
A1	13	0.09	53.8
B	26	0.13	88.5
C	211	0.20	61.1
D	5	0.04	20.0
G	7	0.06	85.7
01_AE	16	n.d.	0.0
02_AG	9	0.79	77.8
07_BC	5	0.04	80.0
08_BC	2	0.97	100.0
A1C	4	n.d.	0.0
A1D	2	0.17	50.0
A1CD	1	0.06	100.0
CD	5	0.11	80.0
All	306	0.18	60.5

* Geometric mean of neutralized viruses.

** IC₈₀ < 20 µg/ml.

Figure 4-6 Summary of 10-1074 neutralizing in vitro activity based on 306 HIV-1 pseudotyped viruses comprising 13 subtypes and recombinant forms. Mean IC₈₀ values are color-coded (dark red: < 0.1 mcg/mL; light red: 0.1 – 0.49 mg/mL; orange 0.5 – 1 mcg/mL; n.d.: not determined) [(36) Suppl]

4.2.4 VRC07-523LS

The VRC, at the NIAID-NIH developed VRC07-523LS, a 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 for both HIV-1 prevention (IND 113,611 and IND 125,494) and therapeutic (IND 126,001, IND 126,664, and IND 113,017) indications. VRC01 was originally isolated from a subject infected with HIV-1 for more than 15 years whose immune system controlled the virus without ART (62, 63). 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 the engineered variant was generated), and later VRC07-523LS (“LS” denotes 2 amino acid mutations), were isolated and subsequently engineered to have potency and breadth greater than those of earlier antibodies (27).

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. The mutations that together define the 523 designation 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 (27). The LS designation specifies methionine to leucine (L) and asparagine to serine (S) (M428L/N434S, referred to as LS) changes within the C-terminus of the heavy chain constant region. The LS mutation was introduced by site-directed mutagenesis to increase the binding affinity for the neonatal Fc-receptor (FcRn); this mutation increases the recirculation of functional immunoglobulin G (IgG) (31, 64), thus, increasing plasma half-life.

VRC07-523LS was found to be 5- to 8-fold more potent than VRC01, with an inhibitory concentration (IC_{50}) < 50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades, and an $IC_{50} < 1$ mcg/mL against 92% of HIV-1 viruses tested (27). In addition, it displayed minimal levels of autoreactivity.

4.3 Trial design rationale

The safety, tolerability, pharmacokinetics, and antiviral activity of the mAbs included in this trial are being evaluated, individually and in some combinations, in ongoing clinical trials (see Section 4.6). Currently, data for VRC07-523LS from VRC 605 (NCT03015181) are being analyzed. The HVTN 127/HPTN 087 study (NCT03387150), which enrolled participants from February to October 2018, is gathering additional data on this mAb. T001 (NCT02960581) is assessing PGT121 alone, while T002 (NCT03205917) is gathering data on PGDM1400 alone as well as in combination with PGT121. The 10-1074 mAb has been evaluated in several phase 1 studies, alone and when administered along with another mAb, 3BNC117 (23, 36-38).

This clinical trial is designed to evaluate the safety and tolerability profile of three different mAbs, each combined with VRC07-523LS. In Groups 1-3, they will be administered in dual combinations via IV. In Group 4, safety and tolerability of 3 mAbs (PGDM1400, PGT 121, and VRC07-523LS) administered via IV will be evaluated. Additionally, this trial will provide an opportunity to evaluate serum mAb concentrations and to assess (in humans) the neutralization profile of these combinations.

Combinations of VRC07-523LS with PGT121 and/or PGDM1400 or 10-1074 have not yet been evaluated in humans. This study is designed to gather safety information on the dual combination groups (PGT121+VRC07-523LS in Group 1, PGDM1400+VRC07-523LS in Group 2, and 10-1074+VRC07-523LS in Group 3) before the triple combination Group 4 (PGDM1400+PGT121+VRC07-523LS) begins enrolling.

Enrollment in Groups 1-3 across all participating CRSs will be restricted to a maximum of 1 participant per day until all 6 participants have been enrolled in each group. Cumulative safety data will be reviewed on a daily basis by HVTN clinical safety staff (ie, Clinical Safety Specialist nurses and physicians) and reviewed at least weekly by the HVTN 130/HPTN 089 PSRT.

At least 2 weeks after the final participant in Groups 1, 2, and 3 completes the Day 0 infusion, the HVTN 130/HPTN 089 PSRT's safety review will determine if Group 4 may begin to enroll. The HVTN 130/HPTN 089 PSRT will request an ad-hoc review of the data by the HVTN SMB in the instance that serious safety events are identified before proceeding to Group 4 (see Section 11.3.3).

Following approval by the PSRT, Group 4 will begin to enroll. Enrollment will be restricted to a maximum of one participant per day for the first 6 participants. Cumulative safety data will be reviewed daily by HVTN clinical safety staff (ie, Clinical Safety Specialist nurses and physicians) and reviewed at least weekly by the HVTN 130/HPTN 089 PSRT.

At least 2 weeks after the 6th participant in Group 4 completes the Day 0 infusion, the HVTN 130/HPTN 089 PSRT's safety review will determine if study product may be administered to the remaining participants in Group 4 (see Section [11.3.3](#)). Cumulative safety data will be reviewed daily by HVTN clinical safety staff (ie, Clinical Safety Specialist nurses and physicians) and reviewed at least weekly by the HVTN 130/HPTN 089 PSRT.

4.3.1 Dose and schedule

The proposed doses and intervals for Groups 1, 2, and 3 are based on preclinical and clinical studies of PGT121, PGDM1400, 10-1074, and VRC07-523LS. The choice of 20 mg/kg dose aligns with ongoing protocols using VRC07-523LS. Data from human studies of VRC01 (65, 66) and VRC01LS (67), and preclinical and clinical studies of VRC07-523LS, including VRC605 and HVTN 127/HPTN 087 were used to determine the doses and intervals for VRC07-523LS in this trial. Similarly, administration doses and intervals for PGT121 and PGDM1400 are based on data from the T001 and T002 clinical trials. The YCO-0899 (NCT02824536) and MCA-0885 (NCT02511990) trials provided the data for the 10-1074 doses selected for this study (see Section [4.6.3](#)).

The dosing schedule in Group 4 was selected based on the PK modeling of each individual mAb contained in the combinations, assuming no drug-drug PK interactions. Predicted serum concentrations of PGT121 and VRC07-523LS following multiple IV infusions at 20 mg/kg every 8 to 20 weeks were generated through Monte Carlo simulations of 1000 hypothetical trial participants based on population PK models of PK data for PGT121, IV PGDM1400, and VRC07-523LS as of June 2018 ([Figure 4-7](#)).

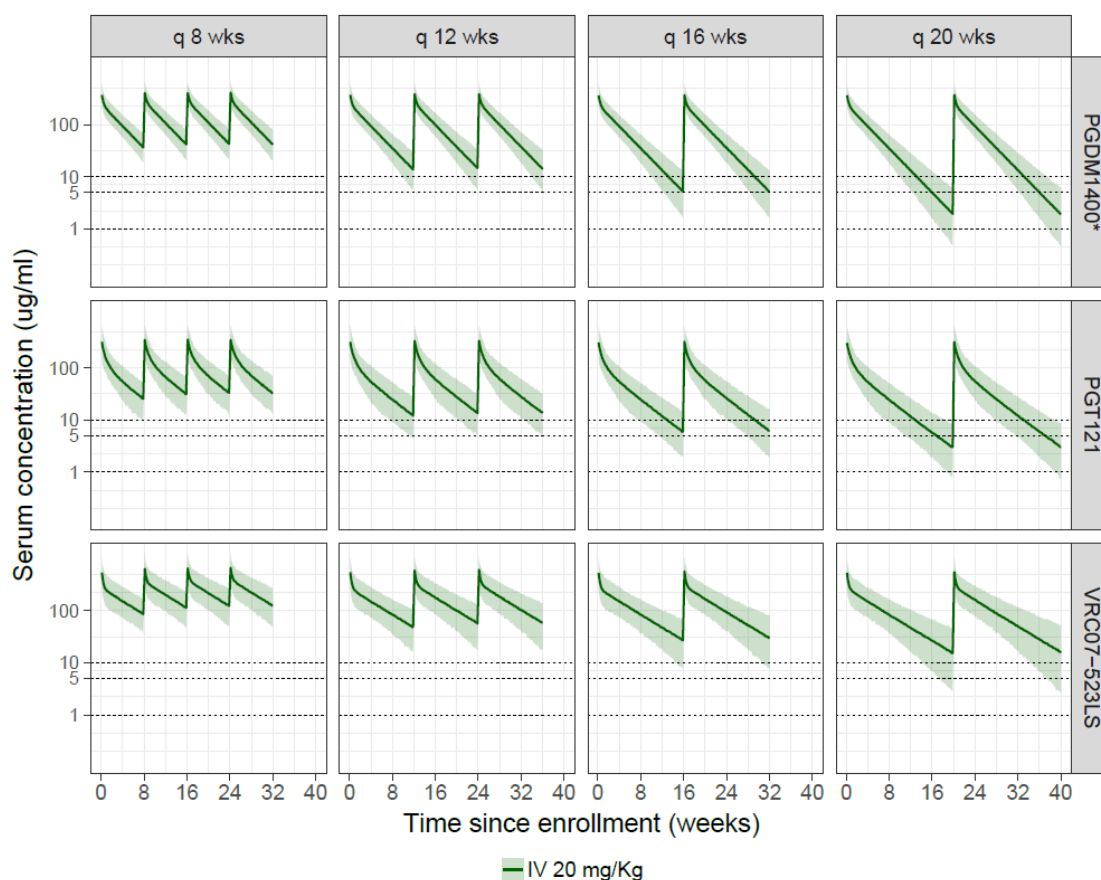


Figure 4-7: Predicted PGDM1400, PGT121 and VRC07-523LS concentration with multiple 8- to 20-weekly IV infusions at 20mg/kg. Shown are median (solid lines), 5th and 95th percentiles (shaded areas) of predicted drug levels with values truncated at half of the lower limit of quantification – 0.12 mcg/mL (PGDM1400), 0.25 mcg/mL (PGT121) or 1.1/2 mcg/mL (VRC07-523LS).

In these simulations, the body weights of the hypothetical trial participants were randomly drawn with replacement from the sample of body weights collected in the HVTN 104 study of VRC01 in US sites, some of which will be used in this study (65, 66). In addition, linear PK was assumed for the mAbs so that PK parameters estimated based on single-dose settings carried forward to multiple-dose settings. The PK parameters used in the simulations were estimated based on observed serum concentration data for PGDM1400 at 3 and 10 mg/kg following a single IV infusion, for PGT121 at 3, 10, and 30 mg/kg following a single IV infusion and at 3 mg/kg following a single SC injection, and for VRC07-523LS at 5, 20, and 40 mg/kg following a single IV infusion, at 20 mg/kg following three 12-weekly IV infusions, at 5mg/kg following a single and at 5 mg/kg following three 12-weekly SC injections. The mean and variance of log-transformed serum concentrations were computed after each IV infusion. Specifically, at 16 weeks after the second IV infusion at a dose level of 20 mg/kg, the serum concentrations (mean \pm SD) were predicted to be 1.6 ± 0.5 for PGDM1400, 1.8 ± 0.5 for PGT121, and 3.4 ± 0.6 for VRC07-523LS. The chance of having a VRC07-523LS serum concentration > 1 mcg/mL at 48 weeks post the second IV infusion at 20 mg/kg is predicted to be about 24%. Given the IC₅₀ and

IC₈₀ data of the mAbs, these PK simulation results suggest that the proposed study design should be able to attain desirable serum concentration levels over time that confer sufficient neutralization against diverse panels of viruses (see Section 4.1). Thus, based on currently available data, in Group 4, a dosing interval of every 16 weeks was selected to have high probability of achieving a trough above 1 mcg/mL for all study mAbs. This threshold of 1 mcg/mL is the limit of detection of the currently used anti-idiotypic enzyme-linked immunosorbent assay (ELISA) for mAb serum concentrations.

Substantial safety data have already been collected over several trials on products related to VRC07-523LS, including VRC01 and VRC01LS. These studies have demonstrated the safety and tolerability of the IV of the individual mAbs at doses similar to or greater than those proposed in this study. For example, in VRC 606 (NCT02599896), the doses for VRC01LS in HIV-uninfected participants ranged between 1 and 40 mg/kg for IV administrations. Moreover, in multiple studies, including VRC 601, VRC 602, HVTN 104, RV397, RV398, A5340, A5342, and P1112, doses for VRC01 in HIV-uninfected and/or HIV-infected participants ranged between 1 and 40 mg/kg for IV administrations.

Given the reassuring safety profile of VRC07-523LS, PGT121, PGDM1400, 10-1074, and similar mAbs given via IV in previous studies and ongoing trials evaluating these mAbs either individually or in combination (see Section 4.6), placebo recipients are not included in this trial.

4.4 Plans for future product development and testing

In light of the genetic diversity of HIV-1, it is prudent to consider using a combination approach. HVTN 130/HPTN 089 is the first in a series of studies that will evaluate whether combining mAbs that target different epitopes on HIV is additive or synergistic (or potentially antagonistic) with respect to PK and neutralization breadth and potency. It is expected that future studies will evaluate mAb combinations incorporating “LS” formulations of these antibodies; this study will generate reference data against which to compare the performance of these LS formulations. In addition, these data will help inform the design of future mAb studies.

4.5 Preclinical studies

4.5.1 Preclinical studies of PGT121

PGT121 has been assessed in a non-Good Laboratory Practice (GLP) pharmacokinetic rat study, a GLP in vitro tissue cross-reactivity (TCR) study, and a GLP repeat dose toxicity study in rats. In the repeat dose toxicity study, animals were given 30 mg/kg or 300 mg/kg intravenously or 30 mg/kg subcutaneously at weekly intervals over a 28-day period. There were minor disturbances in the plasma proteins with higher total protein, albumin, and globulin resulting in a

lower albumin/globulin ratio. There was also transient local microscopic inflammation (fibrosis, mixed cell inflammation) at the injection site following subcutaneous administration, which increased in severity and/or incidence compared to the control animals. The findings resolved after a 4-week treatment-free period. The no-observed-adverse-effect-level (NOAEL) for intravenous administration was 300 mg/kg and for subcutaneous injection was 30 mg/kg, which were the highest dose levels administered.

PGT121 can neutralize a wide array of HIV-1 viruses in vitro and can treat and prevent SHIV in the NHP model. Complete protection from different strains of SHIV was shown with 20 mg/kg and protection in most animals at levels of 5 mg/kg, 1 mg/kg, and 0.2 mg/kg (29). PGT121 administered at 10mg/kg to SHIV-infected animals resulted in rapid virologic control to undetectable levels by day 7 followed by viral rebound between day 42 and day 56 in 3 of the 4 animals after antibody levels declined to undetectable. One animal exhibited long-term control (26).

See the Investigator's Brochure (IB) for further details.

4.5.2 Preclinical studies of PGDM1400

PGDM1400 has been assessed in a non-GLP pharmacokinetic rat study, a GLP in vitro TCR, and a GLP repeat dose toxicity study in rats.

In the repeat dose toxicity study, administration of PGDM1400 alone or in combination with PGT121 by once weekly subcutaneous or intravenous injection for one month (total of 5 injections) at 30 mg/kg/dose, and alone by once weekly intravenous injection at 300 mg/kg/dose, resulted in slightly higher plasma proteins in males, and a higher incidence of hemorrhage at the subcutaneous injection sites that had received PGDM1400. Neither of these findings was considered adverse, and they were not observed after a one-month recovery (treatment-free) period. No clinical signs or local reactions were noted at the injection sites that were considered to be related to the administration of PGDM1400 alone or in combination with PGT121. Body weight, food consumption, hematology, coagulation and urine volume and composition were unaffected by treatment with PGDM1400 alone or in combination. The NOAEL for intravenous administration was 300 mg/kg and for subcutaneous injection was 30 mg/kg, which were the highest dose levels administered.

4.5.2.1 Preclinical challenge study of PGDM1400

PGDM1400 was evaluated against a novel challenge stock, SHIV-325c, developed specifically for NHP challenge studies of PGDM1400, CAP256, and related variants and PGDM1400 demonstrated protection at low doses. As shown in [Figure 4-8](#) below, rhesus macaques received a single IV infusion of PGDM1400 (n = 5 at 2 mg/kg; n = 5 at 0.4 mg/kg; n = 4 at 0.08 mg/kg) 24 hours before high dose intrarectal challenge with SHIV-325c. All animals in the control group were infected between days 7 and 28. In the 2 mg/kg group, one of five

animals receiving PGDM1400 became infected on Day 28; in the 0.4 mg/kg group, no animals became infected; in the 0.08 mg/kg group, three of four animals receiving PGDM1400 were infected. The average serum antibody concentrations in animals administered PGDM1400 at doses of 2, 0.4, and 0.08 mg/kg were 6.9, 2.5, and 0.22 mcg/mL, respectively, at the time of challenge. The half-life of PGDM1400 was calculated for the 2, 0.4, and 0.08 mg/kg groups to be 7.7 days, 6.7 days, and 6.3 days, respectively (47).

See IB for further details.

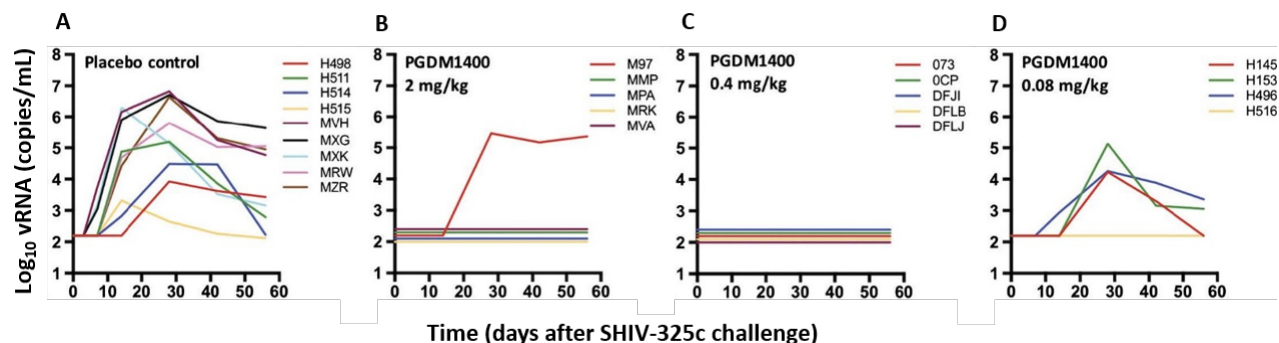


Figure 4-8: Protective efficacy of PGDM1400 against SHIV-325c in rhesus macaques. Plasma viral RNA (as log vRNA copies/mL) is shown for animals that received: (A) saline control; (B) PGDM1400 (2mg/kg); (C) PGDM1400 (0.4 mg/kg); (D) PGDM1400 (0.08 mg/kg). The assay sensitivity limit was >50 RNA copies/mL

4.5.2.2 Preclinical challenge study of PGT121 and PGDM1400

Administration of both PGT121 and PGDM1400 in NHP challenge with a combination of SHIV-SF162P3 (sensitive in vitro to PGT121, resistant to PGDM1400) and SHIV-325c (sensitive in vitro to PGDM1400, resistant to PGT121) demonstrated protection with the combination of the two mAbs, but not with either mAb alone, as reflected in [Figure 4-9](#) (47).

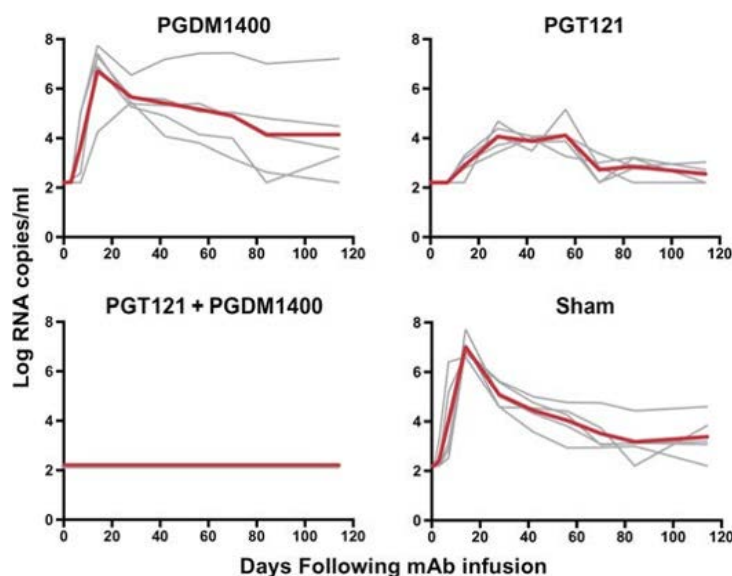


Figure 4-9: Protective efficacy of the combination of PGT121 + PGDM1400 against a mixed SHIV challenge in rhesus monkeys. Five animals per group received an intravenous single dose of PGDM1400, PGT121, the combination of PGT121 + PGDM1400, or saline (Sham) before being rectally challenged with a high dose of both SHIV-SF162P3 and SHIV-325C. Graphs depict the log plasma viral RNA copies/mL after mixed challenge with SHIV-SF162P3 and SHIV-325C. Red line indicates median values. Detection limit is 50 copies/mL.

4.5.3 Preclinical studies of 10-1074

In addition to therapeutic and preventive pharmacology studies in humanized mice (68), the potential of 10-1074 to prevent SHIV infection was evaluated in rhesus macaques (69, 70). A total of 10 rhesus macaques were administered a single IV infusion of 10-1074 at 0.2 mg/kg (n = 2), 1 mg/kg (n = 2), 5 mg/kg (n = 2), or 20 mg/kg (n = 2) dose levels, and challenged intrarectally with SHIV-AD8 or SHIV-CL7 (1000 TCID₅₀) 1 day later. As shown in [Table 4-1](#), passive transfer of 5 mg/kg of 10-1074 protected 2 of 2 animals from SHIV-AD8. When challenged with SHIV-CL7, 1 of 2 animals treated with 1 mg/kg of 10-1074 was protected.

Table 4-1 10-1074 protection against high dose SHIV challenge in rhesus macaques

Dose (mg/kg)	Protected animals after challenge	
	SHIV AD8	R5 SHIV CL7 AD8
20	2/2	2/2
5	2/2	NA
1	0/2	1/2
0.2	NA	0/2

Another NHP study was performed to evaluate the efficacy of a single IV dose (20 mg/kg) of 10-1074 in blocking repeated weekly low dose virus challenge of the clade B SHIV AD8 (10 TCID₅₀) (71). Compared to control animals, which required 2 to 6 challenges (median = 3 weeks) for infection, a single 10-1074 infusion was protective for a median of 12.5 weeks (range 7 to 23 weeks). The

animals were also monitored for safety and no clinical signs were reported after the animals received 10-1074 infusion, including no evidence of altered behavior, decreased appetite, fluctuation in body weight, or development of respiratory or gastrointestinal signs.

See the IB for more details.

4.5.4 Preclinical studies of VRC07-523LS

VRC07-523LS has been assessed in several preclinical safety studies evaluating potential off-target binding, TCR, toxicity, and local tolerance.

VRC07-523LS was found to be 5- to 8-fold more potent than VRC01, with an inhibitory concentration (IC_{50}) < 50 mcg/mL against 96% of HIV-1 pseudoviruses representing the major circulating HIV-1 clades, and an IC_{50} < 1 mcg/mL against 92% of HIV-1 viruses tested. In addition, it displayed minimal levels of autoreactivity.

In vivo proof-of-concept studies showed that VRC07-523LS is about 5-fold more potent than VRC01LS in Rhesus macaques and displays a longer half-life (9.8 days) than VRC07 (4.9 days) after a single dose of mAb at 10 mg/kg administered IV (27).

See the IB for further details.

4.6 Clinical studies

4.6.1 Clinical studies of PGT121

T001 is a phase 1 randomized placebo-controlled clinical trial of the safety, pharmacokinetics, and antiviral activity of PGT121 in HIV-uninfected and HIV-infected adults. The study design is shown below in [Table 4-2](#).

Table 4-2: T001 study schema

	Group	Participants	Sub-Group	Regimen	N	Dose (mg/kg) - administration
Part 1 ⁽¹⁾	1 ⁽³⁾	HIV-uninfected participants	1A	PGT121/Placebo	4/1 (6/2 if DLT ⁽²⁾)	3 IV
			1B	PGT121/Placebo	4/1 (6/2 if DLT)	10 IV
			1C	PGT121/Placebo	4/1 (6/2 if DLT)	30 IV
			1D	PGT121/Placebo	4/1 (6/2 if DLT)	3 SC
	2 ⁽³⁾	HIV-infected on ART, (<50 cp/ml)	2A	PGT121/Placebo	4/1 (6/2 if DLT ⁽²⁾)	3 IV
			2B	PGT121/Placebo	4/1 (6/2 if DLT)	10 IV
			2C	PGT121/Placebo	4/1 (6/2 if DLT)	30 IV
	Safety Monitoring Committee Review ⁽⁴⁾					
Part 2	3 ⁽⁵⁾	HIV-infected off ART (VL 2x10 ³ – 1x10 ⁵ cp/ml)	3A ⁽⁶⁾	PGT121	6 (max 9)	30 IV
			3B	PGT121	8 (max 12)	10 IV
			3C	PGT121	10 (max 15)	3 IV
		HIV-Infected off ART (VL 1x10 ² – 2x10 ³ cp/ml)	3D ⁽⁷⁾	PGT121	3	30 IV
			3E	PGT121	3	10 IV
			3F	PGT121	3	3 IV

DLT, dose limiting toxicity; ART, antiretroviral therapy; cp, copies; ml, milliliter

Administration of PGT 121 will be by intravenous infusion (IV) or subcutaneous injection (SC)

The hypothesis in this ongoing study is that PGT121 administration will be safe by both IV and SC routes. The secondary hypothesis is that PGT121 will be detectable in human sera with a definable half-life. As of June 2018, accrual is complete in Groups 1A-1C (HIV-uninfected, 3-30 mg/kg, IV route), Group 1D (HIV-uninfected, 3 mg/kg, SC route), as well as in Groups 2A (HIV-infected, 3 mg/kg, IV route) and 2B (HIV-infected, 10 mg/kg, IV route). Blinded interim safety data as of June 2018 included all accumulated safety data through week 24 post investigational product administration for Groups 1A, 1B, 1C, 1D, 2A, and 2B. After intravenous administration of 3 mg/kg, 10 mg/kg or 30 mg/kg, there was short-lived, mild or moderate local and systemic reactogenicity. After subcutaneous administration of 3 mg/kg, there was short-lived, mild local reactogenicity but no systemic reactogenicity. There have been no related SAEs. There has been one unrelated SAE (hospital admission for orthopedic surgery). To date, there have been no study safety pauses for AEs and product administrations have been generally well tolerated.

Safety data for Groups 1A, 1B, and 1C was reviewed by the independent Safety Monitoring Committee (SMC) in January 2018. There were no dose limiting toxicities (DLTs), defined as: (1) any grade 3 or greater reactogenicity, or any adverse events judged by the study investigators as at least possibly related to investigational product; or (2) any SAE considered at least possibly related to investigational product), and maximum tolerated dose (MTD) was not reached. The SMC recommended to proceed with enrollment of Group 3 at the maximum dose of 30 mg/kg PGT121.

PGT121 concentrations have been measured in Group 1A (HIV-uninfected, 3 mg/kg, IV route), Group 1B (HIV-uninfected, 10 mg/kg, IV route) and Group 1C (HIV-uninfected, 30 mg/kg, IV route) by validated anti-idiotypic PK and TZM-bl neutralization assays through week 15 postinfusion. As shown in [Figure 4-10](#), the medium half-life of PGT121 during the elimination phase was 23 days, with the half-life ranging from 19 to 26 days. PGT121 neutralizing antibody (nAb) concentrations to X2088_c9 and CNE30 pseudoviruses were significantly and positively correlated with the PGT121 binding Ab concentrations. See the IB for more details.

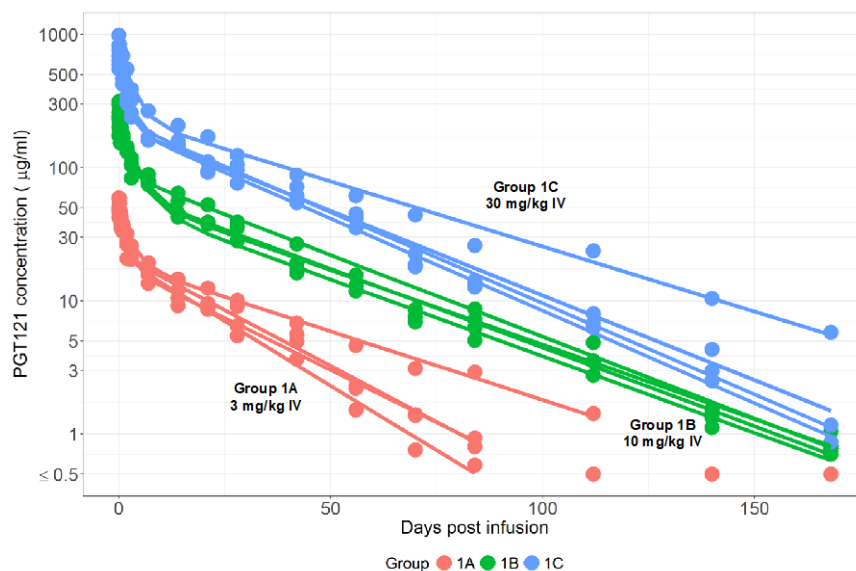


Figure 4-10: PGT121 binding antibody concentrations in Group 1A (HIV uninfected, 3 mg/kg), Group 1B (HIV uninfected, 10 mg/kg) and Group 1C (HIV uninfected, 30 mg/kg).

4.6.2 Clinical studies of PGDM1400 and combination of PGT121 and PGDM1400

T002 is a phase 1 randomized placebo-controlled clinical trial of the safety, pharmacokinetics, and antiviral activity of PGDM1400 as well as the combination of PGDM1400+PGT121 in HIV-uninfected and HIV-infected adults. The study design is shown below in [Table 4-3](#)

Table 4-3: T002 study schema

	Group	Participants	Sub-Group	Regimen	N	Dose (mg/kg)
Part 1 – MTD	1	HIV-uninfected participants	1A	PGDM1400/Placebo	3/1 (6/2 if DLT)	3 IV
			1B	PGDM1400/Placebo	3/1 (6/2 if DLT)	10 IV
			1C	PGDM1400/Placebo	3/1 (6/2 if DLT)	30 IV
				Total Group 1	9/3 = 12 (max 18/6 = 24 if DLT)	
	2	HIV-uninfected participants	2A	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	3 + 3 IV
			2B	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	10 + 10 IV
			2C	PGDM1400 + PGT121/Placebo	3/1 (6/2 if DLT)	30 + 30 IV
				Total Group 2	9/3 = 12 (max 18/6 = 24 if DLT)	
		Total Groups 1 and 2	18/6 = 24 (max 36/12 = 48 if DLT)			
Safety Monitoring Committee						
Part 2 – antiral effect	3	HIV-infected off ART (VL 1x10 ³ – 1x10 ⁵ copies/ml)	3A	PGDM1400	6 (max 18)	MTD IV
			3B	PGDM1400+PGT121	6 (max 18)	MTD IV
				Total Group 3	12 (max 36)	
			Total entire study	36 (max 84)		

DLT, dose limiting toxicity; MTD, maximum tolerated dose

Blinded interim safety data as of October 2018 included all accumulated safety data between 2 and 24 weeks post investigational product administration for Groups 1A (24 weeks), 1B (24 weeks), 1C (16-24 weeks), and 2A (20-24 weeks), 2B (8-16 weeks), and 2C (4-8 weeks). After intravenous administration of 3 mg/kg, 10 mg/kg, and 30 mg/kg of PGDM1400 and after administration of 3+3 mg/kg, 10+10 mg/kg, and 30+30 mg/kg of PGDM1400 and PGT121, there was short-lived, mild or moderate local and systemic reactogenicity. There have been no related SAEs. To date, there have been no study safety pauses for AEs and product administrations have been generally well tolerated.

PGDM1400 concentrations have been measured in Group 1A, 1B, and 1C (HIV-uninfected, 3, 10, and 30 mg/kg, IV route, respectively) by validated anti-idiotypic PK assays through week 4-24 postinfusion. The preliminary medium half-life of PGDM1400 during the elimination phase is 21 days.

As of October 2018, accrual is complete in Groups 1A, 1B, and 1C (HIV-uninfected, PGDM1400 at 3, 10 and 30 mg/kg, respectively, IV route) and in Group 2A, 2B, and 2C (HIV uninfected, PGDM1400+PGT121 at 3+3, 10+10 and 30+30 mg/kg, respectively, IV route). The external SMC reviewed the safety data on October 17, 2018. There were no DLTs, defined as: (1) any grade 3 or greater reactogenicity, or any adverse events judged by the study investigators as at least

possibly related to investigational product; or (2) any SAE considered at least possibly related to investigational product), and MTD was not reached. The SMC recommended to proceed with enrollment of Group 3 at the maximum dose of 30 mg/kg PGDM1400 and 30 mg/kg PGT121. Enrollment into Group 3 (HIV-infected viremic) is ongoing and it is estimated to be completed at the end of March 2019.

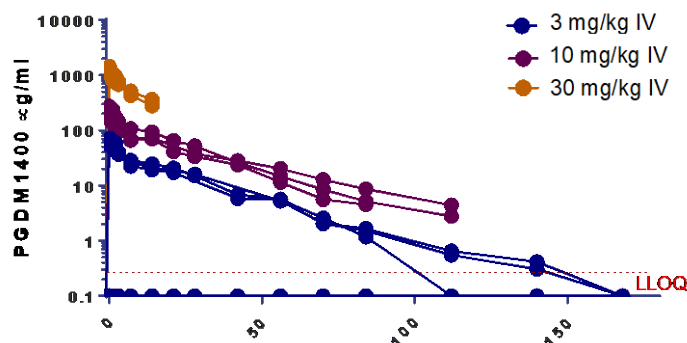


Figure 4-11 PGDM1400 binding antibody concentrations in Group 1A (HIV uninfected, 3 mg/kg), Group 1B (HIV uninfected, 10 mg/kg), and Group 1C (HIV uninfected, 30 mg/kg)

See the IB for more details.

4.6.3 Clinical studies of 10-1074

As of November 2018, 10-1074 had been administered to 92 study participants at doses ranging from 3 mg/kg to 30 mg/kg (32 HIV-uninfected and 49 HIV-infected). 10-1074 has been generally well tolerated at all dose levels tested (ie, 3, 10, and 30 mg/kg).

In a first-in-human, open label, dose-escalation study of 10-1074 (protocol MCA-0885, NCT02511990, see [Figure 4-12](#)), 33 participants (19 HIV-infected and 14 HIV-uninfected) were given 1 IV infusion at 3, 10, and 30 mg/kg. Six participants received 10 mg/kg and 21 received 1 infusion at 30 mg/kg. All study participants were followed to 24 weeks. 10-1074 was generally safe and well tolerated at the doses tested. A total of 57 adverse events were reported during a follow-up period of 6 months, 88% of these were of grade 1 severity. The most commonly reported adverse event deemed possibly related to the study drug was transient, mild headache. There were no serious adverse events, or grade 3 related adverse events.

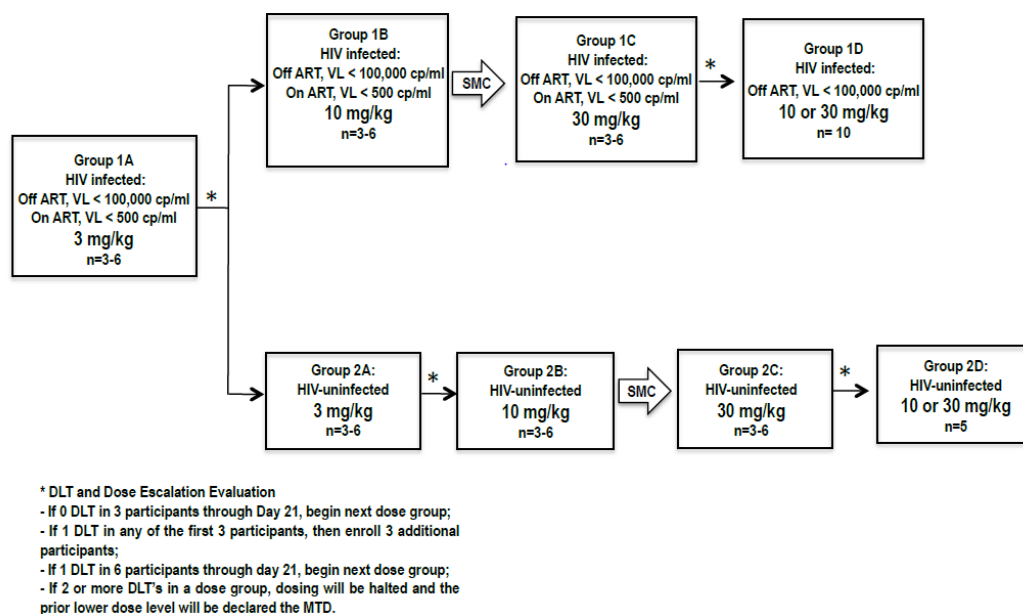


Figure 4-12 MCA-0885 schema

Two phase 1 clinical trials of the combination of the CD4 binding site bnAb 3BNC117 plus 10-1074, administered intravenously, are currently underway. In one study (protocol YCO-0899, NCT02824536, see [Figure 4-13](#)) HIV-uninfected individuals received 1-3 doses of the antibody combination at 3 or 10 mg/kg or placebo. A total 24 of participants enrolled in the study, and 18 received the 3BNC117 and 10-1074 combination (the study is placebo-controlled and remains blinded). In the second study (protocol MCA-0906, NCT02825797, see [Figure 4-14](#)), HIV-infected individuals receive 1 to 3 doses of 3BNC117 and 10-1074 combination at 10 or 30 mg/kg each or placebo. Fifteen study participants discontinue ART and receive up to 3 infusions of the mAbs at weeks 0, 3, and 6. To date, 34 individuals enrolled (30 received the antibody combination and 4 received placebo). Of those, 12 received 3 infusions of 30 mg/kg, administered 3 weeks apart, and 3 received 3 infusions of 30 mg/kg, 2 weeks apart.

There have been no SAEs, and the safety profile of the 3BNC117 plus 10-1074 combination is similar to what was observed with either antibody alone. Most reported AE's were graded as mild (77%), and the most commonly reported AEs were upper respiratory infection, headache, and malaise/fatigue

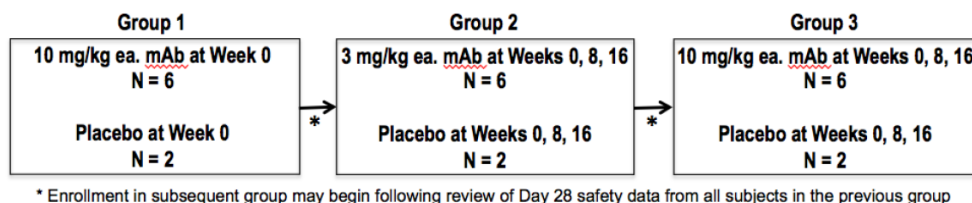


Figure 4-13 YCO-0899 schema

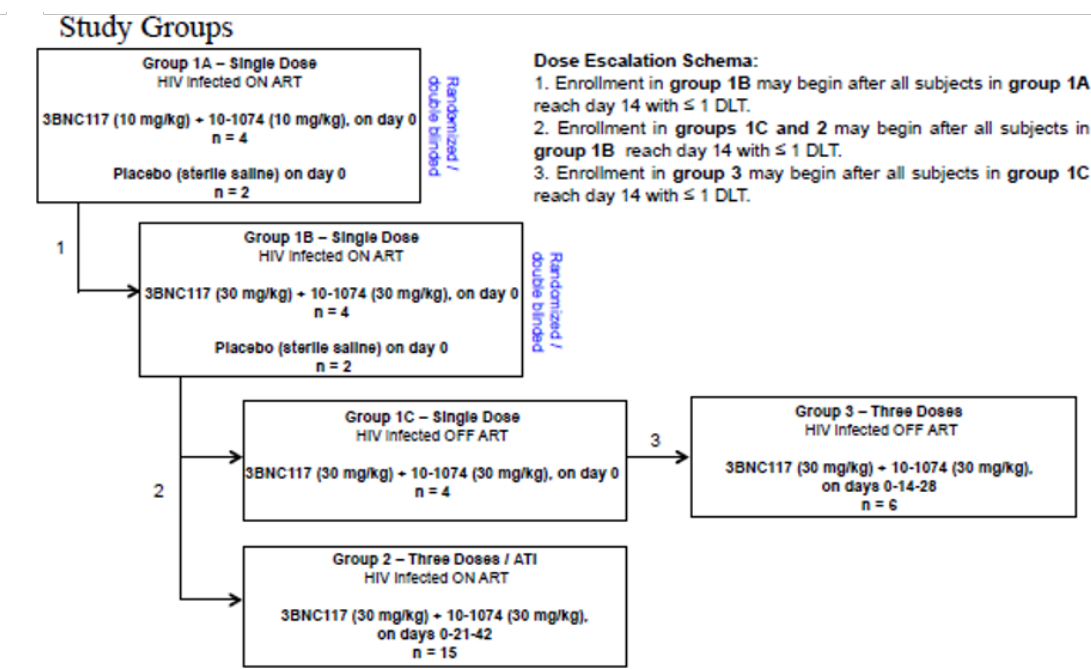


Figure 4-14 MCA-0906 Schema

See the IB for additional details.

4.6.4 Clinical studies of VRC07-523LS

4.6.4.1 VRC 605

A phase 1 open-label, dose-escalation study of VRC07-523LS, VRC 605 (NCT03015181), is 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 (q 12 weeks) of 5 mg/kg SC and 20 mg/kg IV VRC07-523LS (Table 4-4).

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.

Table 4-4 VRC 605 study schema

Group	Participants	Administration Schedule		
		Day 0	Week 12	Week 24
1	3	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			

IV = intravenous infusion

SC = subcutaneous injection

The study is fully enrolled and study product administration is complete. There have been no serious adverse events (SAEs) or safety pauses and product administrations have been generally well tolerated, with no reports of grade 3 or higher related adverse events deemed related to the study product. [Figure 4-15](#) depicts preliminary PK data that suggests pharmacokinetics similar to those of VRC01-LS.

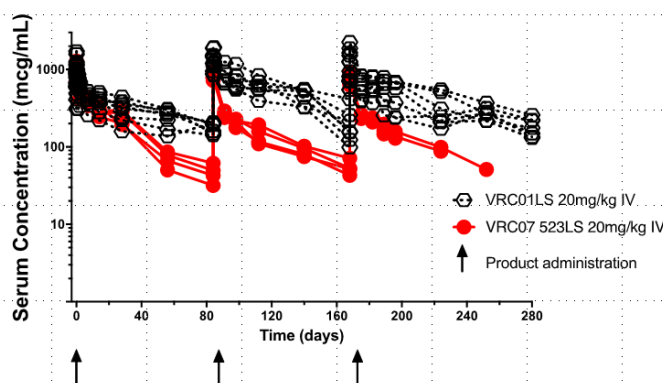


Figure 4-15 Serum concentrations of VRC07-523LS (from VRC 605) after 3 IV infusions of 20 mg/kg. (Confidential–interim and preliminary)

4.6.4.2 HVTN 127/HPTN 087

The follow-up study HVTN 127/HPTN 087 (NCT03387150) is a randomized phase 1 clinical trial that evaluates the safety and serum concentrations of VRC07-523LS administered in multiple doses and routes to healthy, HIV-uninfected adults.

Table 4-5 HVTN 127/HPTN 087 (Version 2.0) study schema

Group	N	Route	Dose	VRC07-523LS 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

Between February and October 2018, HVTN 127/HPTN 087 enrolled a total of 124 healthy, HIV-uninfected adult participants to receive multiple administrations of VRC07-523LS via IV, SC, or IM routes (IM added in protocol version 2.0; 4 IM participants receive placebo). 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 concentration over time for different doses, schedules, and routes of administration. Additional objectives include building a population PK model of VRC07-523LS and determining whether ADA emerge in response to repeated administrations of the antibody.

No Grade 3 or higher AEs deemed related to VRC07-523LS and no serious adverse events (SAEs) have been reported in HVTN 127/HPTN 087. The majority of participants have reported no local or systemic Solicited AEs and no Unsolicited AEs. The few reported Unsolicited AEs have been Grade 1 (mild) and the few reported Solicited AEs have been Grade 1 (mild) or Grade 2 (moderate).

See the IB for more details.

4.7 Potential risks of study products and administration

There is early phase human experience with administration of VRC07-523LS. VRC 605 was evaluating the safety and pharmacokinetics of 1 to 3 administrations of VRC07-523LS prior to the start of HVTN 127/HPTN 087. In addition, the similar CD4-binding site mAb, VRC01, has been given to more than 3000 participants 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 and HVTN 704/HPTN 085. Additionally, both VRC01 and VRC01LS are being tested in an ongoing phase 1 study (HVTN 116).

As of January 2018, the VRC605 study is fully enrolled. Twenty-five of 26 subjects received at least 1 dose of VRC07-523LS (12 SC and 25 IV administrations). One subject withdrew prior to receiving the study product. There have been no SAEs and no safety pauses for AEs. Overall, 15 of 25 subjects who received the product (60%) have had at least one AE with the maximum severity being grade 1 for 7 subjects, grade 2 for 6 subjects, grade 3 for 1 subject and grade 4 for 1 subject. The grade 3 AE was for an elevated creatinine 56 day after the last product administration. This was most likely related to dehydration following exercise. The creatinine value was determined to be a grade 3 based on the DAIDS Grading Table parameter of an increase of 1.5 to 2 times the baseline value, which was still well within the institutional normal range. The grade 4 AE was for elevated liver enzymes likely related to a starting a concomitant medication, fluoxetine, known to cause hepatotoxicity, and not related to VRC07-523LS. VRC07-523LS administrations were discontinued for this subject due to the concomitant illness. While the subject was being followed for safety, liver enzymes tests fluctuated again after starting citalopram which reinforced that the event was most likely caused by an underlying sensitivity to selective serotonin reuptake inhibitor (SSRI) medications. This grade 4 laboratory abnormality was not considered life-threatening, as it was not clinically significant as there were no hospitalization, jaundice, coagulopathy, bleeding, or ascites. Six mild or moderate AEs were assessed as related to study product including mild dizziness, 4 occasions of infusion reactions (1 mild and 3 moderate, reported for 2 subjects), and mild abdominal pain. All AEs assessed as related to the study product have resolved without residual effects.

Two subjects developed infusion reactions shortly after IV product administration. Symptoms were typical of infusion reactions observed with other monoclonal antibodies (72). No atypical symptoms or delayed symptoms were seen. Specifically, one subject enrolled in the 40mg/kg IV group experienced a moderate infusion reaction with chills, rigors, fever, myalgia, and headache beginning 15 minutes after completion of the infusion. The subject was treated with acetaminophen and ibuprofen. All symptoms resolved within 12 hours. Another subject in the 20mg/kg IV group experienced 3 separate infusion reactions (n=2 moderate, n=1 mild) after each product infusion. The subject experienced nausea, chills, rigors, malaise, tachycardia, headache, myalgia, and arthralgia. Symptoms began 15 minutes to 1 hour after completion of each product administration and completely resolved within 12 hours. The subject was treated with acetaminophen and ibuprofen.

Human experience with PGDM1400 and PGT121 is limited to the T001 and T002 clinical trials. As of June 2018, T001 and T002 accrual is ongoing, and there have been no related SAEs. There has been one unrelated SAE (hospital admission for orthopedic surgery) in T001. To date, there have been no study safety pauses for AEs and product administrations have been generally well tolerated.

As of November 2018, 10-1074 has been administered to 92 participants either alone or in combination with 3BNC117 in the MCA-0885, YCO-0899, MCA-

0906, and MCA-965 protocols. 10-1074 has been generally safe and well tolerated at the doses tested. The majority of the reported AEs were graded mild and there have been no SAEs or study safety pauses in either of these clinical trials.

Experience is accruing with each of these mAbs alone and in dual combination mentioned above (Section 4.6) but the current study evaluating 3 mAbs together will be a first in human.

Overall, the side effects of mAbs are mild and can include fever, flushing, chills, rigors, nausea, vomiting, diarrhea, pain, pruritus, rash, urticaria, angioedema, headache, dizziness, shortness of breath, bronchospasm, tachycardia, hypotension, hypertension, and chest pain. There can also be a risk of infection from mAbs targeting human cytokines or human cell antigens, but this is not expected with a mAb targeting a viral antigen (73).

Additional reactions such as tumor lysis syndrome and cytokine release syndrome have been previously described with chimeric and humanized Abs, usually with mAbs targeting human antigens. Cytokine release syndrome has been described with human mAbs targeting lymphocyte cell-surface antigens. Serious allergic reactions such as anaphylaxis, angioedema, bronchospasm, hypotension, and hypoxia are rare and often associated with mAbs targeting human proteins or with non-human mAbs. These mAb-related events typically occur within the first 24 hours of administration. Cytokine release syndrome typically occurs within the first few hours of administration, and usually with the first administration when the largest number of target cells expressing antigen are present. Reactions related to the rate of infusion have been described for several FDA-licensed mAbs. Cytokine release syndrome can be effectively managed by temporarily holding the administration, administering anti-histamines, and restarting the IV infusion at a slower rate (74).

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 to a few weeks after the exposure to the mAb and are noted to be more common with chimeric types of mAb (73, 75).

Other potential side effects of mAbs include thrombocytopenia, autoimmune diseases, cancer, dermatitis, and cardiotoxicity (73).

Since PGT121, PGDM1400, 10-1074, and VRC07-523LS all target a viral antigen rather than human cell surface antigens and are human mAbs, serious infusion reactions are expected to be rare.

There is a possibility that receipt of the study products will cause a reactive result on some currently available HIV test kits, especially if testing occurs close to study product administration timepoints (see Section [9.5.1](#)).

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 (66). The ongoing efficacy trials HVTN 704/HPTN 085 and HVTN 703/HPTN 081 have accumulated significant additional VRC01 clinical experience; however, as these trials remain blinded, they do not yet contribute to the unblinded VRC01 safety profile.

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 intravenous infusion: The placement of an intravenous catheter can allow for the development of bacteremia because of the contact between the catheter and unsterile skin during insertion. Risk of infection from IV infusion will be minimized through careful decontamination of local skin prior to catheter placement and through the use of infection control practices during infusion. The risk of product contamination will be minimized by the use of aseptic technique in the pharmacy and universal precautions during product administration.

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1

To evaluate the safety and tolerability of PGT121 or PGDM1400 or 10-1074 when administered in sequence via IV with VRC07-523LS (2-mAb combinations), and of PGDM1400, PGT121, and VRC07-523LS administered in sequence via IV (3-mAb combination)

Primary endpoint 1

Local and systemic Solicited AEs, laboratory measures of safety, Unsolicited AEs, and SAEs

Early discontinuation of administration and reason(s) for discontinuation and early study termination

Primary objective 2

To evaluate the serum concentrations and pharmacokinetics of PGT121, PGDM1400, 10-1074 and VRC07-523LS after a single 2-mAb administration and after each PGDM1400, PGT121, VRC07-523LS 3-mAb administration

Primary endpoint 2

Serum concentrations of PGT121, PGDM1400, 10-1074, and VRC07-523LS at prespecified timepoints among participants who received all scheduled product administrations

Primary objective 3

To evaluate the individual mAb-specific serum neutralizing activity of PGT121, PGDM1400, 10-1074 and VRC07-523LS after a single 2-mAb administration and after each PGDM1400, PGT121, VRC07-523LS 3-mAb administration

Primary endpoint 3

Magnitude of serum neutralizing activity measured with mAb-specific Env-pseudotyped viruses in TZM-bl cells at prespecified timepoints among participants who received all scheduled product administrations

5.2 Secondary objectives and endpoints

Secondary objective 1

To correlate serum concentrations of PGT121, PGDM1400, 10-1074, and VRC07-523LS with corresponding virus neutralization titers in serum

Secondary endpoints 1

Serum concentrations of PGT121, PGDM1400, 10-1074, and VRC07-523LS at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Magnitude of serum neutralizing activity measured with Env pseudotyped viruses in TZM-bl cells at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 2

To determine whether the mAbs maintain their expected combined magnitude and breadth of serum neutralizing activity after a single 2-mAb administration (Groups 1-3) and after each 3-mAb administration (Group 4) as predicted by the known magnitude and breadth of neutralization of the corresponding mAb combinations as non-infused clinical products

Secondary endpoint 2

Magnitude of neutralizing activity against a panel of Env pseudotyped reference viruses in TZM-bl cells at selected timepoints for all participants in all groups regardless of how many product administrations and how much product they received

Secondary objective 3

To determine whether ADA are present and whether there is a correlation among PGT121, PGDM1400, 10-1074, and VRC07-523LS concentrations and ADA titers in serum samples

Secondary endpoint 3

Serum PGT121, PGDM1400, 10-1074, and VRC07-523LS concentrations and ADA titers in each group measured at prespecified timepoints for all participants in all groups regardless of how many product administrations and how much product they received

5.3 Exploratory objectives

Exploratory objective 1

To determine whether any confirmed positive ADA samples have functional activity that impacts the neutralizing activity of PGT121, PGDM1400, 10-1074, and VRC07-523LS

Exploratory objective 2

To further evaluate non-neutralizing antiviral activities, additional assays (eg, antibody dependent cell mediated cytotoxicity [ADCC], antibody dependent cellular phagocytosis [ADCP], virion capture) may be performed for activities that PGT121, PGDM1400, 10-1074, and VRC07-523LS are shown to exhibit in vitro

Exploratory objective 3

To develop predictive population PK models and to assess PK, drug-drug interaction, and neutralization drug-drug interaction among PGT121, PGDM1400, 10-1074, and VRC07-523LS

Exploratory objective 4

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 enrolling 27 healthy, HIV-uninfected adult participants in four treatment groups. Groups 1, 2, and 3 entail IV administration of VRC07-523LS along with either PGT121, PGDM1400, or 10-1074; Group 4 entails 2 IV administrations of PGDM1400, PGT121, and VRC07-523LS. Groups 1 through 3 will be open label, open to enrollment simultaneously and randomized at a 1:1:1 ratio with $n = 6$ participants per group. Enrollment of Group 4 with $n = 9$ participants will follow the review of safety data in Groups 1-3. To ensure that both persons assigned male sex at birth and persons assigned female sex at birth will be adequately represented, the trial will enroll at least approximately 40% of each.

Since enrollment is concurrent with receiving the first study product administration, all participants will provide some safety data. However, for mAb concentration and antiviral analyses, 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. For this reason, the sample size calculations in Section 6.1.2 account for 15% enrolled participants having missing data for the primary lab endpoint at a given timepoint. As a reference, 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 at a given timepoint. In HVTN 104 (phase 1 trial of VRC01), approximately 10-15% of mAb 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. 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 $n = 6$, there is a 90% chance of observing at least 1 event if the true rate of such an event is 31.9% or more; and there is a 90% chance or more of observing no events if the true rate is 1.7% or less. For Group 4 of size $n = 9$, there is at least a 90% chance of observing at least 1 event if the true rate of such an event is 22.6% or more; and there is at least a 90% chance of observing no events if the true rate is 1.2% or less. For Groups 1-3 combined with $n = 18$, there is at least a 90% chance of observing at least 1 event if the true rate of such an event is 12.0% or more; and there is at least a 90% chance of observing no events if the true rate is 0.6% or less. For all active double- and triple-mAb treatment groups combined, with $n = 27$, there is at least a 90% chance of observing at least 1 event if the true rate of such an event is 8.2% or more; and there is at least a 90% chance of observing no events if the true rate is 0.4% or less. As a reference, in HVTN vaccine trials

from April 2008 through March 2018, about 1.7% 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 6, 9, 18, and 27 are presented in [Table 6-1](#) for a range of possible true adverse event rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with sequential administration of VRC07-523LS with either PGT121, PGDM1400, or 10-1074, or sequential administration of VRC07-523LS, PGT121, and PGDM1400.

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among groups of size 6, 9, 18, and 27 for different true event rates

Group size	True event rate (%)	Pr(0/n ₁)	Pr(1+/n ₁)	Pr(2+/n ₁)
6	1	0.94	0.06	<0.01
	4	0.78	0.22	0.02
	10	0.53	0.47	0.11
	20	0.26	0.74	0.34
	30	0.12	0.88	0.58
9	1	0.91	0.09	<0.01
	4	0.69	0.31	0.05
	10	0.39	0.61	0.23
	20	0.13	0.87	0.56
	30	0.04	0.96	0.80
18	1	0.84	0.16	0.01
	4	0.48	0.52	0.16
	10	0.15	0.85	0.55
	20	0.02	0.98	0.90
	30	<0.01	>0.99	0.99
27	1	0.76	0.24	0.03
	4	0.33	0.67	0.29
	10	0.06	0.94	0.77
	20	<0.01	>0.99	0.98
	30	<0.01	>0.99	>0.99

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval for the true adverse event rate based on the observed data.

[Table 6-2](#) shows the 2-sided 95% confidence intervals for the probability of an event based on a particular observed rate. Calculations are done using the score test method (76). If none of the 27 participants in all treatment groups experiences a safety event, the 95% 2-sided upper confidence bound for the true rate of such events in the total treated population is 12.5%. For each individual antibody treatment arm of $n = 6$ or 9 , the 2-sided upper confidence bound for this rate is 39.0% and 29.9%, respectively.

Table 6-2 Two-sided 95% confidence intervals for the probability of observing a safety event based on observing a particular rate of safety endpoints for arms of size 6, 9, 18, and 27

Observed event rate	95% Confidence interval (%)
0/6	(0.0, 39.0)
1/6	(3.0, 56.4)
2/6	(9.7, 70.0)
0/9	(0.0, 29.9)
1/9	(2.0, 43.5)
2/9	(6.3, 54.7)
0/18	(0.0, 17.6)
1/18	(1.0, 25.8)
2/18	(3.1, 32.8)
0/27	(0.0, 12.5)
1/27	(0.7, 18.3)
2/27	(2.1, 23.4)

6.1.2 Sample size calculations for serum mAb concentrations

Primary objective 2 of this study is to evaluate serum concentrations of VRC07-523LS, PGT121, PGDM1400, and 10-1074 at several timepoints (ie, pharmacokinetics) following IV administration of these mAbs. This objective is descriptive in nature and will be accomplished by estimating the mean serum concentration of each mAb within each treatment group at specific timepoints following each administration. The precision with which a true mean concentration can be estimated from observed data depends on the standard deviation (SD) of the measurements and the sample size. [Table 6-3](#) displays two-sided 95% confidence intervals (CIs) for the mean mAb concentration for several values of the observed average mAb concentration. The construction of these confidence intervals assumed sample sizes of $n = 5$ and 7 per arm, reflecting a missingness rate of 15%, compared to a planned treatment group size of 6 and 9 participants, respectively. The calculations assumed that log-transformed serum concentrations are approximately normally distributed. To account for the small sample sizes, a t-distribution was used to construct CIs. For instance, with an observed mean \log_e serum level of $\log_e(10 \text{ mcg/mL})$ and assuming a standard deviation of 0.5 for their log-transformed values, a two-sided 95% confidence interval for the true mean mAb concentration level is (5.4, 18.6) and (6.3, 15.9) (in $\log_e(\text{mcg/mL})$) with an effective sample size of 5 and 7 participants, respectively. Of note, a SD of less than 1.0 was generally observed in the log-transformed serum concentrations of VRC01 at various timepoints post IV infusions or SC injections of VRC01 in HVTN104 (65).

Table 6-3 Two-sided 95% confidence intervals based on observing a particular average log_e mAb concentration in participants in any of the active arms, taking 15% attrition into consideration (n = 5 or 7)

Observed average log _e -mAb concentration (log _e mcg/mL)	SD of log _e -mAb concentration (log _e mcg/mL)	95% confidence interval (mcg/mL)	
		n = 5	n = 7
log _e (0.5)	0.5	(0.3, 0.9)	(0.3, 0.8)
log _e (1)		(0.5, 1.9)	(0.6, 1.6)
log _e (3)		(1.6, 5.6)	(1.9, 4.8)
log _e (5)		(2.7, 9.3)	(3.1, 7.9)
log _e (10)		(5.4, 18.6)	(6.3, 15.9)
log _e (20)		(10.7, 37.2)	(12.6, 31.8)
log _e (30)		(16.1, 55.8)	(18.9, 47.6)
log _e (40)		(21.5, 74.4)	(25.2, 63.5)
log _e (50)		(26.9, 93)	(31.5, 79.4)
log _e (100)		(53.7, 186)	(63, 158.8)
log _e (250)		(134.4, 465.1)	(157.4, 397)
log _e (500)		(268.7, 930.2)	(314.9, 794)
log _e (1000)		(537.5, 1860.5)	(629.8, 1587.9)
log _e (0.5)	1.0	(0.1, 1.7)	(0.2, 1.3)
log _e (1)		(0.3, 3.5)	(0.4, 2.5)
log _e (3)		(0.9, 10.4)	(1.2, 7.6)
log _e (5)		(1.4, 17.3)	(2, 12.6)
log _e (10)		(2.9, 34.6)	(4, 25.2)
log _e (20)		(5.8, 69.2)	(7.9, 50.4)
log _e (30)		(8.7, 103.8)	(11.9, 75.6)
log _e (40)		(11.6, 138.5)	(15.9, 100.9)
log _e (50)		(14.4, 173.1)	(19.8, 126.1)
log _e (100)		(28.9, 346.1)	(39.7, 252.1)
log _e (250)		(72.2, 865.3)	(99.1, 630.4)
log _e (500)		(144.5, 1730.7)	(198.3, 1260.7)
log _e (1000)		(288.9, 3461.4)	(396.6, 2521.5)

6.1.3 Sample size calculations for serum neutralization activity

Primary objective 3 of this study is to evaluate serum neutralization titers of VRC07-523LS, PGT121, PGDM1400, and 10-1074 against Env-pseudotyped viruses specific to each mAb at several timepoints following IV administrations. This objective is also descriptive in nature, and will be accomplished by estimating, within each treatment group, the mean serum neutralization titers of each mAb against the specific virus. The precision with which a true mean neutralization titer can be estimated from observed data depends on the SD of the measurements and the sample size. [Table 6-4](#) displays two-sided 95% confidence intervals for the mean neutralization titer for several values of the observed average ID₅₀ or ID₈₀ neutralization titer. The construction of these confidence intervals assumed sample sizes of n = 5, and 7 per group, reflecting an attrition

rate of 15% compared to the planned treatment group size of 6 and 9 participants, respectively. The calculations assumed that log-transformed neutralization titers are approximately normally distributed. To account for the small sample sizes, a t-distribution was used to construct CIs. For instance, with an observed mean titer of $\log_e(50)$ and assuming a standard deviation of 0.5 for their log-transformed values, a two-sided 95% confidence interval for the true mean neutralization titer is (26.9, 93) and (31.5, 79.4) with an effective sample size of 5 and 7 participants, respectively. Of note, based on neutralization data against a global panel of 11 pseudoviruses in six participants in HVTN104, an SD of approximately 1.0 was observed in the \log_e -transformed ID₅₀ titers at various timepoints post IV infusions of VRC01(65).

Table 6-4 Two-sided 95% confidence intervals based on observing a particular average \log_e -neutralization titer in participants in any of the active arms, taking 15% attrition into consideration (n = 5 or 7)

Observed average \log_e neutralization titer	SD of \log_e neutralization titer	95% confidence interval	
		n = 5	n = 7
$\log_e(5)$	0.5	(2.7, 9.3)	(3.1, 7.9)
$\log_e(20)$		(10.7, 37.2)	(12.6, 31.8)
$\log_e(50)$		(26.9, 93)	(31.5, 79.4)
$\log_e(100)$		(53.7, 186)	(63, 158.8)
$\log_e(250)$		(134.4, 465.1)	(157.4, 397)
$\log_e(500)$		(268.7, 930.2)	(314.9, 794)
$\log_e(1000)$		(537.5, 1860.5)	(629.8, 1587.9)
$\log_e(5)$	1.0	(1.4, 17.3)	(2, 12.6)
$\log_e(20)$		(5.8, 69.2)	(7.9, 50.4)
$\log_e(50)$		(14.4, 173.1)	(19.8, 126.1)
$\log_e(100)$		(28.9, 346.1)	(39.7, 252.1)
$\log_e(250)$		(72.2, 865.3)	(99.1, 630.4)
$\log_e(500)$		(144.5, 1730.7)	(198.3, 1260.7)
$\log_e(1000)$		(288.9, 3461.4)	(396.6, 2521.5)

6.2 Randomization

A participant's randomization assignment will be computer generated and provided to the CRS pharmacist through a Web-based randomization system. Groups 1, 2, and 3 will be randomized in blocks to ensure balance across groups. The enrollment of Group 4 will be contingent on safety data from Groups 1-3 and hence Group 4 will not be randomized with Groups 1-3.

6.3 Blinding

Participants and CRS staff will be unblinded to participant group assignments. Laboratory program staff will remain blinded during sample analysis.

6.4 Statistical analyses

All safety data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many study product administrations they received. In the rare instance that a participant receives the wrong treatment at a specific study product administration time, the Statistical Analysis Plan (SAP) will address how to analyze the participant's safety data. Analyses of safety data are modified intent-to-treat (MITT) in that individuals who are randomized but not enrolled do not contribute data and hence are excluded. Because of the brief length of time between randomization and enrollment—typically no more than 4 working days—very few such individuals are expected. The primary analysis of mAb concentration and neutralizing activity data are per-protocol (PP) in that only individuals who receive the expected mAb combination at the expected dose level within the expected visit window contribute data. Secondary analysis will also involve the MITT cohort.

Analyses for primary endpoints will be performed using SAS and R. Additional software may be used to perform non-compartmental PK and population PK analyses (eg, NONMEM). All other descriptive and inferential statistical analyses will be performed using SAS, StatXact, or R statistical software.

No formal multiple comparison adjustments will be employed for multiple primary or secondary endpoints. However, multiplicity adjustments will be made for certain primary or secondary endpoint assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple pseudoviruses to determine a positive antiviral activity response). Unless otherwise noted, all statistical tests will be 2-sided and will be considered statistically significant if $p < 0.05$.

6.4.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, serum mAb concentrations, neutralization, and ADA for primary- and secondary-objective analyses.

6.4.2 Baseline comparability

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

6.4.3 Safety/tolerability analysis

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

6.4.3.1 Solicited AEs

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

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.

6.4.3.3 Local laboratory values

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

For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (version specified in SSP/SAP) will be tabulated by treatment arm for each

poststudy product administration timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

6.4.3.4 Reasons for study product administration discontinuation and early study termination

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

6.4.4 Serum concentration and PK analysis

6.4.4.1 Primary analyses of serum concentrations

The primary analysis of serum concentration and pharmacokinetics of the evaluated mAbs (Primary objective 2) will be restricted to participants who received all scheduled administrations per-protocol. Serum concentrations that appear unreliable, or from specimens collected outside of the visit window, or from HIV-infected participants postinfection may be excluded. The primary analysis of serum concentration will be descriptive and will be performed separately for each mAb. A non-compartmental pharmacokinetic analysis will be performed on the concentration data. Pharmacokinetic parameters may include, but are not limited to: area-under-the-curve (AUC), maximum concentration (C_{max}), time to C_{max} (T_{max}), clearance (CL), volume of distribution (Vd), terminal elimination rate constant (λ_z) and the terminal half-life ($T_{1/2}$). Data will be summarized by group and overall for CL, Vd, and $T_{1/2}$. Graphical displays of the data (eg, boxplots, scatterplots, histograms, spaghetti plots) will be generated to visually explore distributional properties of the data as well as potential pairwise associations. These summary statistics and graphical displays may be produced for each treatment arm and each timepoint separately.

6.4.4.2 Exploratory analyses of serum concentrations via population PK models

Population PK (popPK) models of each mAb may be developed to describe the overall kinetics of serum concentration and the variation of the kinetics between and within healthy, HIV-uninfected adults based on non-linear mixed effects models. Data from all enrolled participants will be analyzed regardless of how many administrations and how much mAb dose they received (MITT analysis). Serum concentration data from specimens collected outside of the visit window may be included in popPK analyses that account for the actual specimen collection time, and the actual time and dose amount of each product administration. Since the exact date of HIV infection is unknown, any serum level data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. All data from HIV-infected participants who have no seronegative samples postenrollment may be excluded from the analysis.

The popPK models will describe the pharmacokinetics of each mAb at the individual level using a compartmental approach. Based on a previous population PK analysis of the serum concentrations of VRC01 (65), we anticipate that a two-compartmental model can characterize the kinetics of the serum concentrations of the mAbs. In the event the modeling assumptions appear violated, we will consider other compartmental models. Comparisons of PK parameters across treatment groups will be performed using either likelihood ratio or Wald tests. Estimates of metrics of interest as a function of the PK parameters, including half-life and steady state concentration will be derived from these analyses.

6.4.5 Analysis of neutralization activity and correlation with serum concentrations

6.4.5.1 Primary and secondary analyses of serum neutralization titers

The primary analysis of serum neutralization titers against each mAb-specific virus will be restricted to participants who received all scheduled administrations per-protocol. Serum neutralization titers that appear unreliable, or from specimens collected outside of the visit window, or from HIV-infected participants postinfection may be excluded. This analysis of serum neutralization titers will be descriptive and will be performed separately for each mAb. To address Secondary objective 3, at each specified timepoint, the area-under-the-magnitude-breadth curve (AUC-MB) to a panel of viral isolates (77) will be computed for each participant with evaluable neutralization ID₅₀ or ID₈₀ data, as described in (78). Magnitude–Breadth (M-B) curves may be employed to display individual- and group-level response breadth as a function of magnitude. Response breadth is defined as the percentage of viruses in the panel with neutralization titer above certain thresholds. Two choices are to compare the M-B curves among arms, as follows: a non-parametric Wilcoxon rank sum test on the subject-specific area-under-the M-B curve (AUC M-B) or a Kolmogorov-Smirnov type test on the 2 group-average M-B curves. Simulations can be used to obtain 2-sided p-values for the latter test. Second, a weighted-average score-like variable may be constructed to account for the correlations between virus isolates as an integrated magnitude of responses to multiple isolates. Similar group comparison methods described in the first approach may be adopted. Details of either approach will be described in the SAP.

6.4.5.2 Secondary analyses of correlations between serum concentrations and serum neutralization levels

To address Secondary objective 1, data from all enrolled participants will be analyzed regardless of how many administrations and how much mAb dose they received (MITT analysis). Besides descriptive analyses of the correlations, pharmacodynamics (PD) models based on either linear or non-linear mixed effects models may be performed to characterize the correlation between serum concentration (observed or popPK model-predicted) and serum neutralization against each virus or the AUC-MB of serum neutralization against the panel. Similar to the popPK analysis, data from specimens collected outside of the visit

window may be included in the PK/PD analyses that account for the actual specimen collection time, and the actual time and dose amount of each product administration. Since the exact date of HIV infection is unknown, any serum concentration data from blood draws 4 weeks prior to an infected participant's last seronegative sample and thereafter may be excluded. All data from HIV-infected participants who have no seronegative samples postenrollment may be excluded from the analysis.

6.4.6 Analysis of ADA and other functional activities in serum

For the analysis of ADA (Secondary objective 4), data from enrolled participants will be used regardless of how many administrations they received (MITT). For Exploratory objectives regarding non-neutralizing anti-viral functionality, data from all enrolled participants will be used. Assay results that are unreliable or from HIV-infected participants postinfection will be excluded. Additional exploratory analyses examining the impact of ADA on PK will be described in the SAP.

Univariate and bivariate descriptive analyses of continuous assay data (eg, ADCC) will be performed using mean, median, standard deviation, range, skewness, Spearman's and Pearson's correlation coefficients, for example. Graphical displays of the data based on appropriate techniques (eg, boxplots, histograms, kernel density estimates, probability plots, two- or three-dimensional scatterplots, spaghetti plots) will be generated to visually explore distributional properties of the data as well as potential pairwise associations. Statistics and graphical displays will be produced for each treatment arm across timepoints.

Comparisons of continuous assay data between treatment groups or timepoints will be primarily performed using nonparametric rank-based tests, the Wilcoxon rank-sum test, or Friedman nonparametric two-way analysis of variance (ANOVA). In the event the data appear normally distributed, the results of these tests may be compared to those produced by parametric tests (eg, two-sample t-tests with unequal variances). Appropriate data transformations (eg, square-root, logarithmic) may be applied prior to testing hypotheses in order for key distributional assumptions [eg, normality, homoscedasticity (ie, constancy of variance)] to be satisfied.

Analyses of categorical variables (eg, binary) will be conducted by constructing frequency tables. One such table will be produced for each treatment group and each timepoint. Crude response rates will be presented with their corresponding 95% confidence interval estimates calculated using the score test method (72). Associations between categorical variables will be assessed using Fisher's exact, Barnard's exact, or Chi-squared tests.

Analysis of longitudinal data may be performed using mixed effects models or generalized estimating equations (GEE). These approaches allow describing

outcome responses over several timepoints while accounting for potential inter-subject heterogeneity.

To achieve unbiased statistical estimation and inferences with nonparametric tests and generalized linear models fit by GEE methods, missing data need to be missing completely at random (MCAR). MCAR assumes that missingness does not depend on any observed or unobserved data (ie, the observed data is just a random sample of all the potential data). When missingness is negligible (eg, less than 20%), statistical methods (eg, nonparametric tests and GEE methods) based on the MCAR assumption can be used with limited impact on the analysis.

When the frequency of missing data is more substantial, methods that require the MCAR assumption may give misleading results. In this situation, statistical analyses will be performed based on appropriate modeling assumptions and adjusted using weighting methods, or combined with imputation, under the assumption that the missing data are missing at random (MAR). MAR assumes that the probability of an observation being missing only depends on the observed responses or covariates. Thus, this assumption is less stringent than the MCAR assumption. Weighting adjustments (eg, weighted GEE) and imputation methods are valid under MAR. We will consider including any of the available baseline predictors of the missing outcomes as covariates in statistical models. Please see Little and Rubin [(79), Chapters 1, 3, and 6] for elaborate definitions and examples of missing data mechanisms and Ibrahim et al (80) for a review of missing data methods in clinical studies.

Generalized linear models for response rates will use a binomial error distribution and for quantitative endpoints, a normal error distribution. We will assess repeated functional measurement using linear mixed effects models. If functional activity outcomes are left- and/or right- censored, we will use Hughes' (73) linear mixed effects models to accommodate censoring. In addition, exploratory analyses of repeated functional measurements may be done using weighted GEE (74) methods, which are valid under MAR. We will again consider including any of the available baseline predictors of the missing outcomes as covariates in statistical models.

6.4.7 Analyses prior to end of scheduled follow-up visits

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

6.4.7.1 Safety

During the course of the trial, analyses of safety data will be prepared approximately every 4 months for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 130/HPTN 089 PSRT.

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 other endpoints 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 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 K](#))

Laboratory Inclusion Values

Hemogram/Complete Blood Count

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 feminizing 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 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/mm³
12. **WBC differential** either within institutional normal range or with site clinician approval
13. **Platelets** = 125,000 to 550,000/mm³

Chemistry

14. **Chemistry panel**: **ALT** < 1.25 times the institutional upper limit of normal; **creatinine** \leq institutional upper limit 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 antibodies (anti-HCV)**, or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive

Urine

18. **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 study product administration on the day of initial study product administration. Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.
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 one of the following methods:
 - Condoms (male or female) with or without a spermicide,
 - Diaphragm or cervical cap with spermicide,
 - Intrauterine device (IUD),
 - Hormonal contraception,
 - Tubal ligation,
 - Any other contraceptive method approved by the HVTN 130/HPTN 089 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);
 - Or not be of reproductive potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy or bilateral oophorectomy;
 - Or be sexually abstinent.
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.

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 130/HPTN 089 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-Network HIV antibody testing during the planned duration of the HVTN 130/HPTN 089 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 130/HPTN 089 PSRT will determine eligibility on a case-by-case basis.
7. **Previous receipt of humanized or human mAbs**, whether licensed or investigational; the HVTN 130/HPTN 089 PSRT will determine eligibility on a case-by-case basis.
8. **Previous receipt of monoclonal antibodies VRC01, VRC01LS, VRC07-523LS, PGT121, PGDM1400, or 10-1074**

Immune System

9. **Immunosuppressive medications** received within 30 days before first study product administration (Not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatological condition; or [4] a single course of oral/parenteral prednisone or equivalent at doses < 20 mg/day and length of therapy < 14 days.)
10. **Serious adverse reactions** to VRC07-523LS, PGT121, PGDM1400, or 10-1074 formulation components (acetate, sucrose, polysorbate 80, 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 study product administration, unless eligibility for earlier enrollment is determined by the HVTN 130/HPTN 089 PSRT (for mAb see criterion 7 above)
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 or sub-cutaneous 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 injection or 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.
15. **Any medical, psychiatric, occupational, or skin condition (eg, tattoos)** 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 had 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 exclusionary: 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 clinician (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

7.3 Participant departure from study product administration schedule or withdrawal (Group 4 only)

This section concerns an individual participant's departure from the study product administration schedule. Pause rules for the trial are described in Section [11.4](#).

7.3.1 Delaying study product administrations for a participant

Under certain circumstances, a participant's scheduled study product administration will be delayed. Refer to the HVTN 130/HPTN 089 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 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 reactions
- Intercurrent illness that is assessed by the site principal investigator (or designee) to require delaying product administration. The investigator may consult the HVTN 130/HPTN 089 PSRT.
- Pregnancy: study product administration will be stopped while a participant is pregnant. If the participant is no longer pregnant (as defined by 2 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 130/HPTN 089 PSRT.

Do not administer study product outside the Visit 9 window specified in the Section 9.9. If the study product administration is not completed within this visit window, the participant should continue with remaining study visits.

7.3.2 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 administrations may be granted with the unanimous consent of the HVTN 130/HPTN 089 PSRT)
- Clinically significant condition (ie, a condition that affects the immune system or for which continued study product administrations 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 administration

- Grade 3 clinical AE that is subsequently considered to be related to study product administration with the exception of fever, vomiting, and subjective local and systemic symptoms. For grade 3 infusion site erythema and/or induration, upon review, the HVTN 130/HPTN 089 PSRT may allow continuation of study product.
 - 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 administration. Consultation with the HVTN 130/HPTN 089 PSRT is required prior to subsequent study product administrations following any hypersensitivity reaction associated with study product administration
- Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions)

Participants discontinuing study product for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated (see HVTN 130/HPTN 089 SSP).

Participants diagnosed with HIV infection during the study should be encouraged to participate in follow-up visits as indicated in Section [9.12](#).

7.3.3 Participant termination from the study

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

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

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

8 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Section 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 1 and additional information is given below.

Group 1

Treatment 1 (T1): PGT121 20 mg/kg AND VRC07-523LS 20 mg/kg to be administered IV sequentially in this order at Month 0.

Group 2

Treatment 2 (T2): PGDM1400 20 mg/kg AND VRC07-523LS 20 mg/kg to be administered IV sequentially in this order at Month 0.

Group 3

Treatment 3 (T3): 10-1074 20 mg/kg AND VRC07-523LS 20 mg/kg to be administered IV sequentially in this order at Month 0.

Group 4

Treatment 4 (T4): PGDM1400 20 mg/kg AND PGT121 20 mg/kg AND VRC07-523LS 20 mg/kg to be administered IV sequentially in this order at Month 0 and Month 4.

8.2 Study product formulation

8.2.1 PGT121 (Labeled as PGT121)

PGT121 will be supplied as 10 mL single-use glass vials with 6 mL fill volume, at a concentration of 50 mg/mL. Upon thaw, each vial contains a clear, colorless to slightly yellow solution for injection, which is essentially free from foreign particles. The formulation buffer is composed of 20 mM acetate, 9% w/v sucrose, and 0.008% w/v polysorbate 80 at pH 5.2 in Water for Injection (WFI). It does not contain a preservative.

The product is stored frozen at -25 °C to -15 °C. The study product is described in further detail in the IB.

8.2.2 PGDM1400 (Labeled as PGDM1400)

PGDM1400 will be supplied as 10 mL single-use glass vials with a 6 mL fill volume, at a concentration of 50 mg/mL. Upon thaw, each vial contains a clear, colorless to slightly yellow solution for injection, which is essentially free from foreign particles. The formulation buffer is composed of 20 mM Acetate, 9% w/v Sucrose, 0.008% w/v Polysorbate 80 at pH 5.2 in WFI. It does not contain a preservative.

The product is stored frozen at -25°C to -15°C. The study product is described in further detail in the IB.

8.2.3 10-1074 (Labeled as 10-1074)

10-1074 will be supplied as 50 mL single-use glass vials with a 30 mL fill volume, at a concentration of 20 mg/mL. Upon thaw, each vial contains a clear, colorless to yellow liquid, which is essentially free of visible particles. The formulation buffer is composed of Potassium Phosphate, Monobasic, NF, BP, EP 0.20 mg; Sodium Phosphate, Monobasic, Monohydrate, USP, BP, EP 0.25 mg; Sodium Chloride, USP, FCC 8.00 mg; Potassium Chloride, USP, FCC 0.20 mg; Sodium Phosphate, Dibasic, Heptahydrate, USP, EP 1.67 mg; Polysorbate 80 (plant derived), NF, EP, JP 0.10 mg; and WFI Quality water, USP, q.s. to 1 mL. It does not contain a preservative.

The product is stored at 2°C to 8°C. The study product is described in further detail in the IB.

8.2.4 VRC07-523LS (Labeled as VRC07-523LS HIV MAb Drug Product VRC-HIVMAB075-00-AB)

VRC07-523LS will be supplied as 10 mL single-use glass vials with a 6.25 ± 0.1 mL fill volume and 3 mL single-use glass vials with a 2.25 ± 0.1 mL fill volume, at a concentration of 100 ± 10 mg/mL. Each vial contains a clear, colorless to yellow liquid, essentially free of visible particles; some opaque or translucent particles may be present. The formulation buffer is composed of 50 mM histidine, 50 mM sodium chloride, 5% sucrose, and 2.5% sorbitol at pH 6.8. Vials do not contain a preservative.

VRC07-523LS product label designates the long-term storage as -35°C to -15 °C (-31 °F to 5 °F). The study product is described in further detail in the IB.

8.3 Preparation of study products

Prior to preparation of the first infusion (enrollment visit), a new prescription will be sent to the pharmacy. The prescription **MUST** contain the participant's weight based upon the participant's weight at the most recent visit where weight was measured (this includes screening). If this information is **NOT** on the prescription,

the prescription will be returned to the clinic from the pharmacy to be completed appropriately prior to the pharmacist beginning preparation of study product. Subsequent visit weights (based upon the participant's weight at the most recent visit where weight was measured) must be communicated to the pharmacy in writing prior to the day of the visit. Any changes in weight of more than 10% (between the prior weight and the weight on the day of the infusion visit) will require an updated visit weight communication to the pharmacy in writing so that product can be prepared based on that weight change.

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

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

8.3.1 PGT121

8.3.1.1 Thawing instructions

1. Remove PGT121 vial(s) from freezer and thaw in a room temperature water bath or in a clean beaker/container of water at room temperature, ensuring the vial(s) are not submerged. Swish vial(s) in the water to help facilitate thawing.
2. Once thawed, mix vial contents by gently inverting vial(s) five times.

8.3.1.2 PGT121 intravenous infusion preparation

1. Calculate the total dose (mg) of PGT121 required based on the participant's weight (in kg). Obtain the minimum number of thawed PGT121 vials, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of Sodium Chloride for Injection, 0.9% USP that will also permit the addition of the required calculated volume of PGT121.
2. Using an 18G needle, withdraw the calculated volume of PGT121 into a sterile syringe.
3. Using aseptic technique, add the withdrawn volume of PGT121 to the IV container with 100 mL of Sodium Chloride for Injection, 9.9% USP. **Record this as the study product preparation time. Assign a 4-hour expiration from this time.**
4. Gently mix the prepared IV container. Ensure there are no visible particulates in the IV container.

8.3.2 PGDM1400

8.3.2.1 Thawing instructions

1. Remove PGDM1400 vials from freezer and thaw in a room temperature water bath or in a clean beaker/container of water at room temperature, ensuring the vials are not submerged. Swish vial(s) in the water to help facilitate thawing.
2. Once thawed, mix vial contents by gently inverting vial(s) five times.

8.3.2.2 PGDM1400 intravenous infusion preparation

1. Calculate the total dose (mg) of PGDM1400 required based on the participant's weight (in kg). Obtain the minimum number of thawed PGDM1400 vials, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of Sodium Chloride for Injection, 0.9% USP, that will also permit the addition of the required calculated volume of PGDM1400.
2. Using an 18G needle, withdraw the calculated volume of PGDM1400 into a sterile syringe.
3. Using aseptic technique, add the withdrawn volume of PGDM1400 to the IV container with 100 mL of Sodium Chloride for Injection 0.9% USP. **Record this as the study product preparation time. Assign a 4-hour expiration from this time.**
4. Gently mix the prepared IV container. Ensure there are no visible particulates in the IV container.

8.3.3 10-1074

8.3.3.1 10-1074 intravenous infusion preparation

1. Calculate the total dose (mg) of 10-1074 required based on the participant's weight (in kg). Remove the minimum number of 10-1074 vials from refrigerated storage, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of Sodium Chloride for Injection, 0.9% USP, that will also permit the addition of the required calculated volume of 10-1074.
2. Using aseptic technique, add the withdrawn volume of 10-1074 to the IV container with 100 mL of Sodium Chloride for Injection, 0.9% USP. **Record this as the study product preparation time. Assign a 24-hour expiration from this time.**
3. After product preparation, 10-1074 should be administered within 24 hours, if stored at room temperature.

8.3.4 VRC07-523LS

VRC07-523LS is a highly concentrated protein solution and may develop white, opaque to translucent particles after thawing.

8.3.4.1 Thawing instructions

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 # 4 below.
3. Prior to preparation for administration, swirl vials for 30 seconds to resuspend any visible particles, avoid foaming. **DO NOT SHAKE THE VIALS. If particles are observed, return the vials to 2°C to 8°C storage.** If the particles re-dissolve within the maximum storage times described in # 4 below, they may be used for product preparation. **If particles continue to be observed, do not use the vials.**
4. Thawed 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.

8.3.4.2 VRC07-523LS intravenous infusion preparation

1. Calculate the total dose (mg) of VRC07-523LS required based on the participant's weight (in kg). Remove the minimum number of thawed particle-free VRC07-523LS vials from storage, as well as an appropriately sized IV container (bag/glass bottle) containing 100 mL of Sodium Chloride for Injection, 0.9% USP, that will also permit the addition of the required calculated volume of VRC07-523LS.
2. Gently swirl thawed vials for 30 seconds, avoiding foaming. **DO NOT SHAKE VIALS.** Keep the vials upright at all times until ready to withdraw the contents. Do not invert the vials during inspection.
3. Observe vials for particles. If particles are observed, refer to the thawing instructions described above in Section [8.3.4.1](#).
4. Using aseptic technique, add the calculated volume of VRC07-523 LS to the IV container with 100 mL of Sodium Chloride for Injection, 0.9 USP. **Record this as the study product preparation time.**

5. The prepared VRC07-523LS IV container may be stored at 2°C to 8°C up to 48 hours or at controlled room temperature (maximum 27°C) for a maximum of 4 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 controlled room temperature (maximum 27°C) for a minimum of 30 minutes prior to product administration.

8.3.5 Labeling of Study Product

Label the study product as follows:

- Participant identifier(s)
- Participant weight (in kg)
- Study product name
- Total dose (mg)
- Final volume (mL)
- Infusion time
- Beyond use date and time
- Any additional information required by jurisdiction

8.4 Administration

The container prepared by the pharmacy will include the weight that was used for preparation of the study product. The clinician responsible for administration will check the container label and confirm that the participant identifier(s) is/are correct and that the weight listed on the container label is within 10% of the participant's current actual weight. A filter must be used for product administration. Filters must comply with the specifications described in the HVTN 130/HPTN 089 SSP. When the filter is added to the tubing, prime the administration set with normal saline for injection.

In Groups 1-3, 2 separate IV containers each containing one study product will be administered sequentially. In Group 4, 3 separate containers, each containing one study product, will be administered sequentially.

8.4.1 PGT121

PGT121 will be administered IV over 60 minutes at the Month 0 visit. For participants in Group 4, the subsequent infusion at the Month 4 visit may be administered IV over 30 minutes.

8.4.2 PGDM1400

PGDM1400 will be administered IV over 60 minutes at the Month 0 visit. For participants in Group 4, the subsequent infusion at the Month 4 visit may be administered IV over 30 minutes.

8.4.3 10-1074

10-1074 will be administered IV over 60 minutes at the Month 0 visit.

8.4.4 VRC07-523LS

VRC07-523LS will be administered IV over 60 minutes at the Month 0 visit. For participants in Group 4, the subsequent infusion at the Month 4 visit may be administered IV over 15-30 minutes.

8.5 Acquisition of study products

PGT121 is provided by Beth Israel Deaconess Medical Center (Boston, MA, USA).

PGDM1400 is provided by Beth Israel Deaconess Medical Center (Boston, MA, USA).

10-1074 is provided by the National Institute of Allergy and Infectious Diseases (NIAID), NIH, DHHS (Bethesda, MD, USA).

VRC07-523LS is provided by Dale and Betty Bumpers Vaccine Research Center (VRC), NIAID, NIH, DHHS (Bethesda, MD, USA).

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

Filters, tubing, and 0.9% sodium chloride for injection will be locally sourced by the site. Please refer to the study product considerations section of the HVTN 130/HPTN 089 SSPs for product specific reference numbers.

8.6 Pharmacy records

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

8.7 Final disposition of study products

For US clinical research sites, all unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the study sponsor. For non-US clinical research sites, all unused study products must be destroyed 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 schedules of clinical procedures are shown in [Appendix I](#) and [Appendix J](#).

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 informed consent form (ICF) documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in the study. Informed consent encompasses all written or verbal study information CRS staff provide to the participant, before and during the trial. CRS staff will obtain informed consent of participants according to HVTN and HPTN policies and procedures.

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

A CRS may employ recruitment efforts prior to the participant consenting. For example, some CRSs use a telephone script to prescreen people before they come to the clinic for a full screening visit. Participants must sign a screening or protocol-specific consent before any procedures are performed to determine eligibility. CRSs must submit recruitment and prescreening materials to their 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 prior to implementation at a site.” CRSs are responsible for knowing the requirements of their applicable REs.

9.1.1 Screening consent form

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

Some 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, 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. Sample protocol-specific consent forms for the main study are located in [Appendix A](#) and [Appendix B](#). A separate sample consent form for other uses of specimens is located in [Appendix D](#).

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

- CRS's IRB/EC and any applicable REs,
- 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 sites-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 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 is 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 study product administration on day 0. 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 K](#)).
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots
- Laboratory tests including:
 - Screening HIV
 - Hepatitis B surface antigen (HBsAg),
 - Anti-HCV Abs,
 - Syphilis,
 - Complete Blood Count (CBC) with differential,
 - Chemistry panel (alanine aminotransferase [ALT], creatinine),
 - Urine dipstick (urinalyses if indicated; see Section [9.7](#)),

- Urine or serum pregnancy test (volunteers who were assigned female sex at birth); persons who are not of reproductive potential due to having undergone total hysterectomy with bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing;
- 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 9.5
- 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 or HPTN study

If a participant screens for an HVTN or HPTN study at the same CRS but then does not join that study, screening results from that effort may be applied to the screening for this protocol, as long as the screening was done under participant consent, the participant has signed a consent form to begin screening for this study, and the tests were conducted within the time periods specified in the eligibility criteria (see Sections 7.1 and 7.2).

9.3 Enrollment and study product administration visits

Enrollment is simultaneous with first study product administration. The CRS requests the randomization assignment via a Web-based randomization system. In general, the time interval between randomization and enrollment should not exceed 4 working days. However, circumstances may require a participant's enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all study product administration 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 baseline Solicited AEs;
- Assessment of concomitant medications (as described in Section 9.2);
- Assessment of any new AEs/intercurrent illnesses; and
- Clinical laboratory tests including:
 - CBC with differential;
 - Chemistry panel (see Section 9.2), and
 - Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing;

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

Administration of all infusions during a study product administration visit must be accomplished within 1 calendar day.

Immediately following study product administration, the participant remains in the clinic for observation for 1 hour. At the end of this 1-hour observation period, samples are drawn for PK testing (see Appendix G and Appendix H).

See the HVTN 130/HPTN 089 SSP for details regarding infusion visit protocols and subsequent infusion observation and Solicited AE assessment procedures that CRSs must follow. The site will make arrangements to be in contact with the participant following the Solicited AE period (as described in Section 9.8 and the HVTN 130/HPTN 089 SSP).

The following procedures will be performed at all study product administration visits. These procedures may be performed prior to or following study product administration:

- Risk reduction counseling (as described in Section 9.5);

- For participants capable of becoming pregnant, contraception status assessment (as described in Section 9.2 and 9.6). In persons who are confirmed pregnant, contraception status assessment is not required; and
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation).

The following procedure will be performed at all infusion visits following study product administration:

- Acceptability questionnaire.

Additional procedures will be performed at scheduled visits as specified in [Appendix I](#) and [Appendix J](#):

- Specimen collection (should be completed per [Appendix G](#) and [Appendix H](#)).
- HIV infection assessment including pretest counseling and HIV testing. 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,

9.3.1 Managing infusion reactions

Since PGT121, PGDM1400, 10-1074, and VRC07-523LS are human mAbs that target a viral antigen rather than human cell surface antigens, serious mAb reactions are expected to be rare. Nevertheless, participants will be closely monitored in the clinic during study product administration and during a post-infusion observation period. CRS staff are trained to recognize suspected mAb reactions and to provide immediate medical care consistent with CRS SOP. Medications used to treat mAb reactions may include: acetaminophen, antihistamines, and corticosteroids. CRSs are also equipped with additional emergency medical supplies to provide immediate medical interventions and are near medical emergency services. Should the need arise, CRSs may transfer the participant, once stabilized, to a tertiary care center for further management.

The following procedures should be performed after a mAb reaction:

- mAb reaction clinical assessment;
- mAb reaction blood collection.

For detailed instructions regarding management of mAb reactions see the HVTN 130/HPTN 089 SSP.

9.4 Follow-up visits

The following procedures are performed at scheduled follow-up visits as specified in [Appendix I](#) and [Appendix J](#):

- Risk reduction counseling (as described in Section [9.5](#));
- Contraception status assessment (as described in Section [9.2](#) and [9.6](#)); and
- Administration of behavioral risk assessment questionnaire
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Assessment of new or continuing concomitant medications (as described in Section [9.2](#)); and
- Assessment of new or unresolved Unsolicited AEs/intercurrent illnesses;
- 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);
- HIV infection assessment including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Abbreviated physical examination including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Specimen collection (should be completed per [Appendix G](#) and [Appendix H](#));
- Clinical laboratory tests including:
 - CBC with differential,
 - Chemistry panel (see Section [9.2](#)), and

- Urine dipstick (urinalysis if appropriate; see Section [9.7](#)); and
- Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. During follow-up in persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated.

9.4.1 Interim contacts

CRSs may report safety information obtained at a contact other than the regularly scheduled visits. These contacts are reported as interim visits.

9.5 HIV counseling and testing

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

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

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 [9.12](#).

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.

9.5.1 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 130/HPTN 089 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.

9.6 Contraception status

Contraception status is assessed and documented at clinic visits indicated in [Appendix I](#) and [Appendix J](#) 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.

Self-reported infertility—including having reached menopause (no menses for 1 year) or having undergone hysterectomy or bilateral oophorectomy—must be documented in the participant's study record.

9.7 Urine testing

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

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

Follow-up visit dipstick testing 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. If a follow-up visit dipstick or micro-urinalysis is abnormal due to infection, provide appropriate treatment and/or referral and document this in the participant's source documentation. See the Urinalysis Sample Collection, Interpretation, Management, and Reporting section in the Ab MOP for further details.

9.8 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 9-1](#). Participants are instructed to record symptoms using a Participant Diary. CRS staff and the participant will be in contact after the 3-day Solicited AE assessment period, or sooner if indicated. See the HVTN 130/HPTN 089 SSP 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 9-1](#). 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 to DAIDS criteria, are recorded on an AE Log.

Table 9-1 Schedule of Solicited AE assessments

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

^a Day of study product administration

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

9.8.1 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 CRS staff, not 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 HVTN 130/HPTN 089 SSP).

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.

9.8.2 Assessment of infusion site

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

9.9 Visit windows and missed visits

Target visit windows for follow-up visits have been chosen to ensure the viability of robust PK calculations and cross-protocol comparison. As such, Visits 3 and 4 should be done on Day 3 and 6 on target days; target windows for Visit 5 through visits 24 weeks after the final infusion (ie, Visit 11 for Groups 1-3 and Visit 13

for Group 4) are ± 3 days. The target window expands to ± 7 days for all remaining follow-up visits. The target window for the second infusion visit in Group 4 (Visit 9) is ± 7 days. Broader allowable visit windows are shown below:

- For Groups 1-3: Visit 3 (-2, +1 day(s)), Visit 4 (± 2 days), Visits 5, 6, 7, 9, and 11 (± 7 days), and Visits 12, 13, and 14 (± 14 days)
- For Group 4: Visit 3 (-2, +1 day(s)), Visit 4 (± 2 days), Visits 5, 6, 7, 8, 10, 11, 12, and 13 (± 7 days), and Visits 9, 14, 15, and 16 (± 14 days)

All follow-up visits should take place within the target visit windows. The expanded allowable visit windows may be utilized only if the visit cannot be scheduled within the target visit window. Visits scheduled outside the allowable visit windows are considered protocol deviations. Visit windows are defined in greater detail in the HVTN 130/HPTN 089 SSP.

If a participant misses a scheduled visit, the CRS staff should attempt to bring the participant in as soon as possible to complete the required safety assessments and other procedures. The procedures for documenting missed visits and out of window visits are described in the HVTN 130/HPTN 089 SSP.

If a missed visit required study product administration or if study product administration must be permanently discontinued, please refer to Section [7.3.2](#) for resolution.

9.10 Early termination visit

In the event of early participant termination, site staff should attempt to complete the following assessments, as appropriate: a final physical examination, clinical laboratory tests (including urine dipstick, CBC with differential, and chemistry panel), pregnancy testing, social impact assessment, and HIV test (note, for persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated). For participants who have a confirmed diagnosis of HIV infection, see Section [9.12](#).

9.11 Pregnancy

If a participant becomes pregnant during the course of the study, infusions of study product will not be given, but remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. During follow-up in persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated. 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, refer to Section [7.3.1](#). If the participant is no longer pregnant, refer to Section [7.3.2](#).

See Pregnancy Management and Reporting section of the Ab MOP for further details.

9.12 HIV infection during the study

If a participant becomes HIV-infected during the course of the study, no additional study product will be administered. Participants will be encouraged to continue scheduled study visits for up to 16 weeks following their last study product administration or their last scheduled protocol clinic visit, whichever comes first. Follow-up duration for participants diagnosed with HIV infection may be adjusted in consultation with the CRS investigator and the HVTN 130/HPTN 089 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At postinfection follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected (note: for persons who are confirmed pregnant, pregnancy testing is not required, unless clinically indicated); in addition, some clinic procedures may be modified or discontinued (see [Appendix G](#), [Appendix H](#), [Appendix I](#), and [Appendix J](#)). These individuals may also be referred to appropriate ongoing clinical trials or observational studies.

See the HIV Infection section in the Ab MOP for further details.

10 Laboratory

10.1 CRS laboratory procedures

The HVTN 130/HPTN 089 Site Lab Instructions and HVTN 130/HPTN 089 SSP 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 G](#) and [Appendix H](#), and. 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 G](#) and [Appendix H](#). Not shown is any additional blood volume that would be required if a safety lab needs to be repeated, or if a serum pregnancy test needs to be performed. The additional blood volume would likely be minimal. The total blood volume drawn for each participant will not exceed 500 mL in any 56-day (8-week) period.

10.3 PGT121, PGDM1400, 10-1074, and VRC07-523LS concentrations

PGT121, PGDM1400, 10-1074, and VRC07-523LS concentrations will be measured in serum collected at prespecified timepoints. A quantitative immunoassay will be used to determine the concentration of each mAb. Ultra-sensitive bead-based analyses enable a broad dynamic range and higher sensitivity (eg, for the anti-idiotypic mAb, 5C9, the lower limit of quantification is approximately 50 pg/mL). The operational sensitivity of the quantitative assays will be determined for the clinical grade PGT121, PGDM1400, 10-1074, and VRC07-523LS used for this study. For multiplexed PK measurements, interference testing will be included as part of the qualification/validation. The mAb concentrations may be normalized relative to total protein.

10.4 Neutralizing antibody assay

HIV-1–specific nAb assays will be performed on serum samples from study participants taken at post administration timepoint(s) and at baseline. The TZM-bl

assay will test neutralization of a panel of mAb-specific viruses (one virus per mAb). The assay will also test the neutralization of a panel of viruses that exhibit a range of known sensitivities to mAbs VRC07-523LS, PGDM1400, PGT121, and 10-1074. These viruses will be selected from a global panel and/or clade-specific panels (77, 81) and may be modified by site-directed mutagenesis to be capable of measuring the activity of each mAb individually.

10.5 ADA detection assay

A tiered testing approach will be used to identify and characterize ADAs that may arise. Anti-PGT121, PGDM1400, 10-1074, and VRC07-523LS antibody detection assays (screening, confirmatory, and/or titration) will be performed on serum samples from study participants at indicated timepoints.

10.6 ADA functional assay

A functional ADA assay will be used to characterize any positive activity that is observed in the ADA detection assay. Functional activity will measure a reduction in VRC07-523LS, PGDM1400, PGT121 and 10-1074 neutralizing activity against a qualified virus in the TZM-bl assay.

10.7 Monoclonal Ab 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 130/HPTN 089 SSP for more information.

10.8 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.

10.9 Specimen storage and other use of specimens

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

Other use of specimens is defined as studies not covered by the protocol or the informed consent form for the main study (see [Appendix D](#)).

This research may relate to HIV, vaccines, monoclonal antibodies, 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 ("other use") will occur only after review and approval by the HVTN, the HPTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs/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 CRS in a Web-based tool that documents their current decisions for other use of their specimens. The Networks will only allow other research to be done on specimens from participants who allow such use.

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.

10.10 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 130/HPTN 089 PSRT

The HVTN 130/HPTN 089 PSRT is composed of the following members:

- DAIDS medical officer representatives
- Protocol chairs
- Protocol Team leaders
- Core medical monitor
- Clinical safety specialist

The clinician members of HVTN 130/HPTN 089 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, clinical data manager, study product developer representative, clinical trial manager, clinical research manager, and others may also be included in HVTN 130/HPTN 089 PSRT meetings.

11.1.2 HVTN SMB

The SMB is a multidisciplinary group consisting of biostatisticians, clinicians, and experts in HIV vaccine and drug research that, collectively, has experience in the conduct and monitoring of vaccine, mAb, and other 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 adverse events requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 130/HPTN 089 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 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 130/HPTN 089 PSRT and HVTN SMB (see Section 11.1.2);

The roles and responsibilities of the HVTN Clinical Safety Specialist (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 130/HPTN 089 PSRT AE review criteria (see Section 11.4);
- Notifying CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.4);
- Querying CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 130/HPTN 089 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 HVTN 130/HPTN 089 SSP for further details regarding Solicited and Unsolicited AEs.

The study Unsolicited AE reporting period comprises the entire study period for each individual participant (from enrollment through the last scheduled clinic visit or participant early termination from the study).

All AEs are graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-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 130/HPTN 089 SSP);
- Infusion or Injection Site Erythema or Redness and Infusion or Injection Site Induration or Swelling will not consider surface area and interference with usual social and functional activities such that:
 - Grade 1 is: 2.5 to < 5 cm in diameter;
 - Grade 2 is: ≥ 5 to < 10 cm in diameter;
 - Grade 3 is: ≥ 10 cm in diameter 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);
- mAb reactions not represented in the DAIDS Table to be graded per the "infusion related reaction" row from the Common Terminology Criteria for Adverse Events (CTCAE) from the US DHHS (Version 5.0. Published November 27, 2017, available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf; see also HVTN 130/HPTN 089 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); (2) if the AE meets the criteria for a safety pause/prompt AE review (see Section 11.4).

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/hvtn130hptn089>). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, clinical safety staff will reply within one business day. Serious events that meet pause rule criteria will be addressed immediately (as outlined in [Table 11-1](#)). If email service is not available, the CRS should notify clinical safety staff of the event by telephone, and then submit CRFs.

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

11.2.3 Expedited reporting of adverse events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 (January 2010) of the *Manual for Expedited Reporting of Adverse Events to DAIDS* (DAIDS EAE Manual), which is available on the RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>. 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 <https://rsc.niaid.nih.gov/clinical-research-sites/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 products for which expedited reporting are required are:

- VRC-HIVMAB075-00-AB (VRC07-523LS)
- PGT121
- PGDM1400
- 10-1074

While the participant is in the study, 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.

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not routinely be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment. In addition, the NIAID/DAIDS or designee(s) will prepare and file expedited reports to other appropriate regulatory authorities within the timelines required by pertinent national regulatory agencies.

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

11.3 Safety reviews

11.3.1 Initial safety evaluation

Enrollment in Group 1-3 across all participating CRSs will be restricted to a maximum of 1 participant per day until 6 participants have been enrolled in each group. The HVTN 130/HPTN 089 PSRT will review the cumulative safety data including at minimum local and systemic Solicited AE data reported for the first 72 hours post study product administration on each of these 18 participants.

11.3.2 Safety evaluation for opening enrollment in Group 4

In addition to monitoring participant safety throughout the study period, the HVTN 130/HPTN 089 PSRT will review all cumulative safety data available from Groups 1 through 3 up to and including the 2-week visit after the first study product administration. Based on the assessment of this safety data, the HVTN 130/HPTN 089 PSRT will make a decision regarding the appropriateness of opening enrollment in Group 4. The HVTN SMB may perform an additional review of this safety data to make the final determination based on safety for proceeding to Group 4.

If any Grade 3 or higher AEs deemed related to study product are reported in Groups 1, 2 or 3, the HVTN SMB will perform an additional review of these safety data to make the final determination based on safety for proceeding to Group 4.

11.3.3 Safety considerations for Group 4

In addition to monitoring participant safety throughout the study period, the HVTN 130/HPTN 089 PSRT will review cumulative safety data available on the first 6 participants in Group 4 up to and including the 2-week visit after the first study product administration to determine whether the remaining participants in Group 4 can be enrolled. If any Grade 3 or higher AEs deemed related to study

product are reported in Group 4, the HVTN SMB will perform an additional review of these safety data to make the final determination based on safety for proceeding with enrollment of the remaining 3 participants in Group 4. The HVTN 130/HPTN 089 PSRT may consult with the HVTN SMB on an ad hoc basis for these evaluations.

11.4 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 130/HPTN 089 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 130/HPTN 089 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	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/hvtn130hptn089>).

^b HVTN CSS or HVTN Core designee

^c Does not include subjective Solicited AEs (infusion site pain, 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 130/HPTN 089 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating CRSs. When an immediate safety pause is triggered, HVTN Core notifies the SMB.

Once a trial is paused, the HVTN 130/HPTN 089 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 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 130/HPTN 089 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 130/HPTN 089 PSRT notification or prompt HVTN 130/HPTN 089 PSRT AE review is triggered, HVTN Core notifies the HVTN 130/HPTN 089 PSRT as soon as possible during working hours (local time)—or, if the information was received during off hours, by the morning of the next workday. If a prompt HVTN 130/HPTN 089 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

The HVTN and HPTN require that each CRS submit to its IRB/EC and 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). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 130/HPTN 089 PSRT (see Section [11.5.2](#)).

11.5 Review of cumulative safety data

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

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

11.5.1 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 130/HPTN 089 PSRT AE review criteria.

11.5.2 Weekly review

During the study product administration phase of the trial, the HVTN 130/HPTN 089 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. Following the visit 4 weeks after the final study product administration, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 130/HPTN 089 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the CRS clinic coordinator for verification.

11.6 Study termination

This study may be terminated early by the determination of the HVTN 130/HPTN 089 PSRT, FDA, NIH, Office for Human Research Protections (OHRP), or study product developer(s). In addition, the conduct of this study at an individual CRS may be terminated by the determination of the IRB/EC and any applicable RE.

12 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with the principles of GCP (ICH6), and according to DAIDS, HVTN and HPTN policies and procedures as specified in the network-specific Manuals 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;
- Unblinding of staff and participants;
- Quality control;
- Protocol monitoring and compliance;
- Advocacy and assistance to participants regarding negative social impacts associated with the trial;
- Risk reduction counseling;
- Specimen collection, processing, and analysis;
- Exploratory and ancillary studies and sub-studies, and
- Destruction of specimens.

Any policies or procedures that vary from DAIDS, HVTN, or HPTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 130/HPTN 089 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 I](#) and [Appendix J](#)). A social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to their individual requirements. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety 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 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 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 Network protocols via clarification memos, letters of amendment, or full protocol amendments.

The version history of, and modifications to, Protocol HVTN 130/HPTN 089 are described below.

Protocol history and modifications

Date: March 18, 2019

Protocol version: 1.0

Protocol modification: NA

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 Centers for Disease Control (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 <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>
- Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Published November 27, 2017. Available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HPTN Certificate of Confidentiality
- HVTN 130/HPTN 089 Special Instructions. Accessible through the HVTN protocol-specific website.

- HVTN 130/HPTN 089 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN 130/HPTN 089 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 <https://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.
- National Institutes of Health (NIH) Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research. Available at <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html>
- Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks, July 2008.
- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at <https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf>
- Title 21, Code of Federal Regulations, Part 50. Available at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50>
- Title 45, Code of Federal Regulations, Part 46. Available at <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>

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

15 Acronyms and abbreviations

Ab	antibody
ADA	anti-drug antibodies
ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ART	antiretroviral therapy
AUC	area-under-the-curve
AUC-MB	area-under-the-magnitude-breadth curve
β-HCG	beta human chorionic gonadotropin
bnAb	broadly neutralizing HIV-1 antibody
BP	British Pharmacopoeia
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CI	confidence interval
C _{max}	maximum concentration
CMV	cytomegalovirus
CRF	case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS	clinical research site
CSS	Clinical Safety Specialist
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
DLT	dose limiting toxicity
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
ELISA	enzyme-linked immunosorbent assay
EP	European Pharmacopoeia
FCC	Food Chemical Codex
FcRn	Fc-receptor
FDA	US Food and Drug Administration

Fred Hutch	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GEE	generalized estimating equation
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
IB	Investigator's Brochure
IC	inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	immunoglobulin G
IND	Investigational New Drug
IoR	Investigator of Record
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
JP	Japanese Pharmacopoeia
LOC	Leadership Operations Center
mAb	monoclonal antibody
MAR	missing at random
M-B	Magnitude-Breadth
MCAR	missing completely at random
MITT	modified intent-to-treat
MOP	Manual of Operations
MTD	maximum tolerated dose
nAb	neutralizing antibody
NAEPP	National Asthma Education and Prevention Program
NF	(US) National Formulary
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NIH	US National Institutes of Health
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drugs
OHRP	US Office for Human Research Protections
PAB	DAIDS Pharmaceutical Affairs Branch
PCR	polymerase chain reaction
PD	pharmacodynamics
PK	pharmacokinetic

popPK	population PK (pharmacokinetic)
PP	per-protocol
PSRT	Protocol Safety Review Team
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SD	standard deviation
SDMC	statistical and data management center
SHIV	simian-human immunodeficiency virus
SMB	Safety Monitoring Board
SMC	Safety Monitoring Committee
SPT	DAIDS Safety and Pharmacovigilance Team
SSP	Study Specific Procedures
SSRI	selective serotonin reuptake inhibitor
SUSAR	sudden unexpected serious adverse reaction
TB	tuberculosis
TCR	tissue cross reactivity
T _{max}	time to C _{max}
USP	United States Pharmacopeia
UW-VSL	University of Washington Virology Specialty Laboratory
Vd	volume of distribution
VRC	Vaccine Research Center (NIAID)
WFI	Water for Injection

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Appendix A Sample informed consent form for Groups 1-3

Title: A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in healthy, HIV-uninfected adult participants

Protocol number: HVTN 130/HPTN 089

Site: [Insert site name]

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

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

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN) and [Insert site name] are doing a study to test the combination of different antibodies against HIV. 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. Officially approved antibodies have been used successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 27 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.

There are a total of 4 groups in this study. About 18 people total will take part in Groups 1, 2, and 3. After we see the safety results from Groups 1-3, we will decide whether or not to do Group 4. If we decide to do Group 4, 9 more people will join.

You are being invited to join Group 1, 2, or 3 of the study.

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

- Are the study antibodies safe to give to people in combinations?

- Are people able to take the study antibodies without becoming too uncomfortable?
- How much of the antibodies remains in the body as time passes?
- How does the body's response to the antibodies change depending on the combination given?

2. The study antibodies cannot give you HIV.

The study antibodies are not made from actual HIV. It is impossible for the antibodies to give you HIV. Also, they cannot cause you to give HIV to someone else. We do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. These study antibodies are experimental.

The formal names of the study antibodies are VRC07-523LS, PGDM1400, PGT121, and 10-1074. From here on, we will call them the study antibodies. They are experimental products. That means we do not know if they will be safe to use in people, or if they will work to prevent HIV infection. These study antibodies are used only in research studies.

The different study antibodies were developed by researchers at the Dale and Betty Bumpers Vaccine Research Center in Bethesda, Maryland, the Beth Israel Deaconess Medical Center in Boston, Massachusetts, and the Rockefeller Institute in New York, New York.

In laboratory studies, these study antibodies attached to and prevented infection by many kinds of HIV viruses from around the world. Each of the study antibodies was strongest against different varieties of HIV viruses. When combined in lab tests, they were able to prevent almost all varieties of HIV from infecting human cells.

In animal studies, the study antibodies prevented animals from infection with animal viruses that are very similar to HIV. The study antibodies have also been tested for safety in the laboratory and in animal studies.

We do not know if the study antibodies will prevent HIV infection when given to people. It will take many studies to learn if they will be useful for prevention of HIV infection. This study will not answer these questions.

These study antibodies have been tested in small numbers of people in previous studies. Although there are other ongoing studies using these antibodies individually and in other combinations, there have been no studies in people using the same combinations of two antibodies as in this study. There have not been any serious health problems in any of these studies so far.

Risks of the study antibodies:

This section lists the side effects we know about when the antibodies are given individually. There may be side effects that we don't yet know about, or side effects from these combinations, even serious ones. We will tell you about any new information that might change your willingness to stay in this study.

VRC07-523LS

The VRC07-523LS study antibody was given by injection or intravenous infusion (IV) to 25 people in a clinical trial at the NIH Clinical Center in Bethesda, Maryland. Two people who got the study antibody by IV had chills, fever, nausea, body aches, rapid heartbeat, and headache. These feelings went away within 12 hours.

As of October 2018, about 120 more people have gotten this study antibody by IV or injection in a clinical trial called HVTN 127/HPTN 087. This study is taking place at clinics in the US and in Switzerland. In this study, this antibody has not made people too uncomfortable or caused serious health problems so far.

A similar study antibody called VRC01 has been given to more than 3000 adults in several studies. Many of these studies are still going on and we don't know which people got the study antibodies and which got a placebo (a liquid with no antibody in it). After receiving the IV infusion or injection, many people said they had mild pain, itching, or redness where the antibody or placebo was given to them. Some of these people said they felt like they had the flu after getting the IV or injections, but this feeling lasted a few hours at most.

PGT121

The PGT121 study antibody is being tested in a study with HIV-positive and HIV-negative participants. As of July 2018, about 20 HIV-negative people and 14 HIV-positive people have gotten different doses of the study antibody by IV infusions and injections. Eight other people have gotten a placebo. There have been no serious health problems in any of the participants, and people have not found getting this study antibody or placebo too uncomfortable.

PGDM1400 and PGT121

The PGDM1400 study antibody is being tested by itself and in combination with the PGT121 study antibody. As of October 2018, 9 HIV-negative people have gotten PGDM1400 and 9 more HIV-negative people have gotten both PGDM1400 and PGT121. Six other people in this study have gotten a placebo. In this study people get the different doses of the study antibodies or a placebo by IV infusion. No serious health problems have been reported so far.

10-1074

The 10-1074 study antibody has been tested by itself and in combination with another study antibody. As of November 2018, 32 HIV-negative people have gotten different doses of 10-1074 by IV infusion. The most common problems people reported were upper respiratory tract infections (colds) and headaches. Only a few of these problems were possibly related to getting the study antibody. Most problems were mild.

General risks of antibodies:

There are different types of antibodies officially approved for use in preventing or treating other diseases. From all of these uses of antibodies, we know that most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, fatigue, flushing, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat, or chest pain.

Rarely, some antibodies have caused serious reactions that may be life-threatening. These reactions may include:

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

These rare reactions have not been seen in other studies with similar experimental antibodies.

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

These rare side effects and reactions have not been seen in other studies with the antibodies in this study with 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 the study antibodies will stay in the body. We don't know yet how long they 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 other 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. Being in more than one study may not be safe.

Also during the study, you should not donate blood or tissue.

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

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

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

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

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

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also test you for syphilis, 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 have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

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

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 C, Approved birth control methods (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the study antibodies could affect the developing baby. You must agree to use effective birth control from 21 days before your infusion until 12 months after your study product administration. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

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

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

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

Most of the visits will be 1-2 months apart. We will also ask you to come to the clinic about 3 days, 6 days, and 2 weeks after the infusion visit to draw your blood. We will do this so that we can look at how your body responds to the study antibodies. We will also look at how much of the antibodies are in your blood. The infusion visit can last from [#] to [#] hours. Follow-up 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 female participants 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 some combination of two of the study antibodies.

People in Groups 1, 2, and 3 will get an IV infusion with different combinations of 2 study antibodies.

When getting an IV infusion, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small container of fluid that contains the study antibody. Each antibody is in a separate container. An IV pump controls how fast the fluid drips from the container, through the tube, into your arm. The infusion will take about one hour for each study antibody (total of 2 hours).

Which group you are in and which antibody combination you get is completely random, like flipping a coin. We have no say in which group you are assigned to. Neither do you. You will know which antibody combination you will get.

11. We will give you the study antibodies on a schedule.

You will get the antibodies in a vein in your arm at one visit during the study. The antibodies will be given one at a time.

Site: A picture of IV infusion placement has been provided in Appendix E. You may insert it below or give it as a separate document to volunteers if you believe it will be helpful to them. You are not required to do either.

Infusion Schedule			
Group	Number of Participants	Study Antibodies	IV Infusion
1	6	PGT121 and VRC07-523LS	At enrollment
2	6	PGDM1400 and VRC07-523LS	
3	6	10-1074 and VRC07-523LS	

You will have to wait in the clinic for at least an hour after the infusion to see if there are any problems. We will collect a blood sample one hour after the IV. Then 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 about how to contact you. We will contact you about 3 days after the infusion visit 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
- Ask questions about your experience getting infusions
- 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 25 mL and 100 mL (a little less than 2 tablespoons to a little less than ½ cup). Your body will make new blood to replace the blood we take out. Please tell us if you have blood drawn for other purposes during this study.

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 AF**, Tables of procedures (for informed consent form) in this section or distribute it as a separate sheet if it is helpful to your study participants. You are not required to do either.*

We will be looking for side effects. 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 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.

14. We will test your samples to see how your immune system responds to the study antibodies.

We will send your samples (without your name) to labs approved by the HVTN and HPTN 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 and HPTN in other countries for research related to this study.

The samples will be tested to:

- Measure how much antibody is in your blood, and
- See how your immune system responds to the study antibodies.

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 positive, 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).

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 with your permission.

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

15. When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers.

These samples are called “extra samples”. The HVTN and HPTN 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 or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we 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 and HPTN. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN will send your samples to the researcher’s location.

What information is shared with HVTN, HPTN 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, monoclonal antibodies, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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.

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

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

Your study records and samples will be kept in a secure location. We will label all of your samples and most of your records with a code number, not your name or other personal information. However, it is possible to identify you, if necessary.

We will not share your name with the lab that does the tests on your samples, or with anyone else who does not need to know your name.

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

- The US National Institutes of Health and its study monitors,
- The US Food and Drug Administration,
- 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 Dale and Betty Bumpers Vaccine Research Center, the Beth Israel Deaconess Medical Center, the Rockefeller Institute, and people who work for them,
- The HVTN, HPTN and people who work for them,
- The HVTN Safety Monitoring Board and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

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

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

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

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

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

research, we cannot withhold information from it. Also, you can still release information about yourself and your study participation to others.

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

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

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.

17. We may stop your infusion or take you out of the study at any time. We may do this even if you want to stay in the study.

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you 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 infusion, we may ask you to stay in the study to complete other study procedures.

18. We will not give you an infusion if you become pregnant.

However, if you become pregnant after your infusion, 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.

19. If you get infected with HIV during the study, we will take fewer samples, and we will help you get care and support.

We will encourage you to stay in the study for up to 4 months 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

20. 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:

Collection of blood samples can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, blood clots, and (rarely) muscle damage, or infection. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of getting an IV infusion:

Getting an infusion 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.

Personal problems/discrimination/testing HIV antibody positive:

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

HIV testing

HIV antibody tests are the usual way to test for HIV infections. We have used several common HIV antibody tests to test samples of blood containing different amounts of one of the study antibodies, VRC07-523LS. These tests show that very high levels of this antibody 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. We don't know if the different brands of tests will have similar results for the other antibodies.

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

Because of these risks, you should 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 not HIV infected. We do not expect you to have any problems with HIV testing after the study ends because the antibodies do not last in the body for that long.

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

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

Benefits

21. The study may not benefit you.

We do not expect that getting the study antibodies will 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 gets approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

22. 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

23. 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

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

Your health is important to us. <i>(Sites: adjust the following 2 sentences if applicable to the care available at your site)</i> 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 antibodies and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

Some of the study product providers may pay medical costs for study-related injuries that are determined to be caused by their own study antibodies. If provider funds are not available or are not enough, or if the injury is determined to be caused by study procedures, the HVTN has limited funds to pay medical costs 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/or 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

25. 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.

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

Your permissions and signature

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

26. In Section 14 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 and HPTN 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.

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 or genome wide studies.

27. 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
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*Witness is impartial and was present for the entire discussion of this consent form.

Appendix B Sample informed consent form for Group 4

Title: A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in healthy, HIV-uninfected adult participants

Protocol number: HVTN 130/HPTN 089

Site: [Insert site name]

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

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

About the study

The HIV Vaccine Trials Network (HVTN), the HIV Prevention Trials Network (HPTN) and [Insert site name] are doing a study to test the combination of different antibodies against HIV. 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. Officially approved antibodies have been used successfully to prevent or treat some other health problems, such as a virus that causes respiratory infections in infants.

About 27 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.

There are a total of 4 groups in this study. About 18 people participated in Groups 1, 2, and 3. The results showed that it is safe to move ahead with Group 4, so 9 more people will join.

You are being invited to join Group 4 of the study.

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

- Are the study antibodies safe to give to people in combinations?
- Are people able to take the study antibodies without becoming too uncomfortable?

- How much of the antibodies remains in the body as time passes?
- How does the body's response to the antibodies change depending on the dose and combination given?
- Does the method of giving the antibodies change the body's response?

2. The study antibodies cannot give you HIV.

The study antibodies are not made from actual HIV. It is impossible for the antibodies to give you HIV. Also, they cannot cause you to give HIV to someone else. We do not know if the antibody will decrease, increase, or not change your chance of becoming infected with HIV if you are exposed to the virus.

3. These study antibodies are experimental.

The formal names of the study antibodies are VRC07-523LS, PGDM1400, and PGT121. From here on, we will call them the study antibodies. They are experimental products. That means we do not know if they will be safe to use in people, or if they will work to prevent HIV infection. These study antibodies are used only in research studies.

The different study antibodies were developed by researchers at the Dale and Betty Bumpers Vaccine Research Center in Bethesda, Maryland, the Beth Israel Deaconess Medical Center in Boston, Massachusetts, and the Rockefeller Institute in New York, New York.

In laboratory studies, these study antibodies attached to and prevented infection by many kinds of HIV viruses from around the world. Each of the study antibodies was strongest against different varieties of HIV viruses. When combined in lab tests, they were able to prevent almost all varieties of HIV from infecting human cells.

In animal studies, the study antibodies prevented animals from infection with animal viruses that are very similar to HIV. The study antibodies have also been tested for safety in the laboratory and in animal studies.

We do not know if the study antibodies will prevent HIV infection when given to people. It will take many studies to learn if they will be useful for prevention of HIV infection. This study will not answer these questions.

These study antibodies have been tested in combinations of two Groups 1 through 3 of this study, as well as in small numbers of people in previous studies. Although there are other ongoing studies using these antibodies individually and in other combinations, there have been no studies in people using the same combinations of three antibodies as in this study. There have not been any serious health problems in any of these studies so far.

Risks of the study antibodies:

This section lists the side effects we know about when the antibodies are given individually. There may be side effects that we don't yet know about, or side effects from the combinations, even serious ones. We will tell you about any new information that may change your willingness to stay in this study.

VRC07-523LS

The VRC07-523LS study antibody was given by injection or intravenous infusion (IV) to 25 people in a clinical trial at the NIH Clinical Center in Bethesda, Maryland. Two people who got the study antibody by IV had chills, fever, nausea, body aches, rapid heartbeat, and a headache. These feelings went away within 12 hours.

As of October 2018, about 120 more people have gotten this study antibody by IV or injection in a clinical trial called HVTN 127/HPTN 087. This study is taking place at clinics in the US and in Switzerland. In these studies, this antibody has not made people too uncomfortable or caused serious health problems so far.

A similar study antibody called VRC01 has been given to more than 3000 adults in several studies. Many of these studies are still going on and we don't know which people got the study antibodies and which got a placebo (a liquid with no antibody in it). After receiving the IV infusion or injection, many people said they had mild pain, itching, or redness where the antibody or placebo was given to them. Some of these people said they felt like they had the flu after getting the IV or injections, but this feeling lasted a few hours at most.

PGT121

The PGT121 study antibody is being tested in a study with HIV-positive and HIV-negative participants. As of July 2018, about 20 HIV-negative people and 14 HIV-positive people have gotten the different doses of the study antibody by IV infusions and injections. Eight other people have gotten a placebo. There have been no serious health problems in any of the participants, and people have not found getting this study antibody or placebo too uncomfortable.

PGDM1400 and PGT121

The PGDM1400 study antibody is being tested by itself and in combination with the PGT121 study antibody. As of October 2018, 9 HIV-negative people have gotten PGFM1400 and 9 more HIV-negative people have gotten both PGDM1400 and PGT121. Six other people in this study have gotten a placebo. In this study people get the different doses of the study antibody or a placebo by IV infusion. No serious health problems have been reported so far.

General risks of antibodies:

There are different types of antibodies officially approved for use in preventing or treating other diseases. From all of these uses of antibodies, we know that most side effects happen within the first 24 hours. Those antibodies have caused fever, chills, shaking, nausea, vomiting, pain, headache, dizziness, flushing, trouble breathing, high or low blood pressure, itchiness, rash, hives, lip or face swelling, diarrhea, racing heartbeat, or chest pain.

Rarely, some antibodies have caused serious reactions that may be life-threatening. These reactions may include:

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

These rare reactions have not been seen in other studies with similar experimental antibodies.

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

These rare side effects and reactions have not been seen in other studies with the antibodies in this study with 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 the study antibodies will stay in the body. We don't know yet how long they 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 other 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. Being in more than one study may not be safe.

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
- Looking at your skin
- Listening to your heart and lungs
- Feeling your abdomen (stomach and liver)
- Checking your veins to see how easy it might be to start an IV

We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are. We will also test you for syphilis, 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 have had your uterus or ovaries removed (a hysterectomy or oophorectomy), verified by medical records, you are not required to have a pregnancy test.

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

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 C, Approved birth control methods (for sample informed consent form), in this consent form, paste it below and delete paragraph below.

You should not become pregnant during the study because we do not know how the study antibodies could affect the developing baby. You must agree to use effective birth control from 21 days before your first infusion until 12 months after your last infusion visit. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you.

Being in the study

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

8. You will come to the clinic for scheduled visits about [#] times over about a year and a half.

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

Most of the visits will be 1-2 months apart. We will also ask you to come to the clinic about 3 days, 6 days, and 2 weeks after the first infusion visit to draw your blood. We will do this so that we can look at how your body responds to the study antibodies. We will also look at how much of the study antibodies are in your blood. Infusion visits can last from [#] to [#] hours. Follow-up 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 female participants 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 a combination of three study antibodies.

When getting an IV infusion, a sterile needle is used to place a small plastic tube into a vein in your arm. The tube is connected to a small container of fluid that contains the study antibody. An IV pump controls how fast the fluid drips from the container, through the tube, into your arm. Each antibody is in a separate container. At the first visit, the infusion will take about one hour for each study antibody (total of about 3 hours). Other IV infusions will take about 30 minutes for each study antibody (total of about 1.5 hours).

11. We will give you the study antibodies on a schedule.

You will get antibodies at two visits during the study. The infusions will go into a vein in your arm. The antibodies will be given one at a time.

Site: A picture of IV infusion placement has been provided in Appendix E. You may insert it below or give it as a separate document to volunteers if you believe it will be helpful to them. You are not required to do either.

Infusion schedule				
Group	Number of people	Study Antibodies	Infusion (at enrollment)	Infusion (Month 4)
4	9	PGDM1400, PGT121, and VRC07-523LS	IV	IV

After each set of infusions, you will have to wait in the clinic for at least an hour to see if there are any problems. We will collect a blood sample one hour after the IV. Then 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 about how to contact you. We will contact you about 3 days after each infusion visit 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
- Ask questions about your experience getting infusions
- 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 25 mL and 100 mL (a little less than 2 tablespoons to a little less than ½ cup). Your body will make new blood to replace the blood we take out. Please tell us if you have blood drawn for other purposes during this study.

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

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

We will be looking for side effects. 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 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.

14. We will test your samples to see how your immune system responds to the study antibodies.

We will send your samples (without your name) to labs approved by the HVTN and HPTN 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 and HPTN in other countries for research related to this study.

The samples will be tested to:

- Measure how much antibody is in your blood, and
- See how your immune system responds to the study antibodies.

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).

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 with your permission.

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

15. When samples are no longer needed for this study, the HVTN and HPTN may want to use them in other studies and share them with other researchers.

These samples are called "extra samples". The HVTN and HPTN 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 or HPTN sell my samples and information? No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we 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 and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.] IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN will send your samples to the researcher's location.

What information is shared with HVTN, HPTN 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, monoclonal antibodies, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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.

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

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

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

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

- The US National Institutes of Health and its study monitors,
- The US Food and Drug Administration,
- 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 Dale and Betty Bumpers Vaccine Research Center, the Beth Israel Deaconess Medical Center, the Rockefeller Institute, and people who work for them,
- The HVTN, HPTN and people who work for them,
- The HVTN Safety Monitoring Board and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

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

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

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

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

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

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

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

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.

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

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you 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.

18. We will stop your infusions 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.

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

We will encourage you to stay in the study for up to 4 months after your last infusion visit 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

20. 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:

Collection of blood samples can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, blood clots, and (rarely) muscle damage or infection. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Risks of getting an IV infusion:

Getting an infusion 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.

Personal problems/discrimination/testing HIV antibody positive:

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

HIV testing

HIV antibody tests are the usual way to test for HIV infections. We have used several common HIV antibody tests to test samples of blood containing different amounts of one of the study antibodies, VRC07-523LS. These tests show that very high levels of this antibody 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. We don't know if the different brands of tests will have similar results for the other antibodies.

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

Because of these risks, you should 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 not HIV infected. We do not expect you to have any problems with HIV testing after the study ends because the antibodies do not last in the body for that long.

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

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

Benefits

21. The study may not benefit you.

We do not expect that getting the study antibodies will 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 gets approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

22. 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

23. 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@hvtm.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

24. 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 antibodies and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

Some of the study product providers may pay medical costs for study-related injuries that are determined to be caused by their own study antibodies. If provider funds are not available or are not enough or if the injury is determined to be caused by study procedures, the HVTN has limited funds to pay medical costs 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/or 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

25. 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.

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

Your permissions and signature

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

26. In Section 14 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 and HPTN 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.

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 or genome wide studies.

27. 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
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*Witness is impartial and was present for the entire discussion of this consent form.

Appendix C Approved birth control methods for persons assigned female sex at birth (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 from 21 days before your first study infusion until 12 months after your last infusion.

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 reached menopause, with no menstrual periods for one year;
- You have had a hysterectomy (your uterus removed);
- You have had your ovaries removed;
- You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes;
- 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 infusion.

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

Title: A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in healthy, HIV-uninfected adult participants

Protocol number: HVTN 130/HPTN 089

Site: [Insert site name]

When samples are no longer needed for this study, the HVTN and HPTN may 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. 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 or HPTN sell my samples and information?

No, but the HVTN and HPTN may share your samples with other researchers. Once we share your samples and information, we 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 and HPTN. Also, the researcher's institutional review board (IRB) or ethics committee (EC) will review their plan. *[Site: If review by your institution's IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the HVTN will send your samples to the researcher's location.

8. What information is shared with HVTN, HPTN 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, monoclonal antibodies, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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 and HPTN

keep 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.

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 or genome wide studies.

Participant's name (print)	Participant's signature or mark	Date	Time
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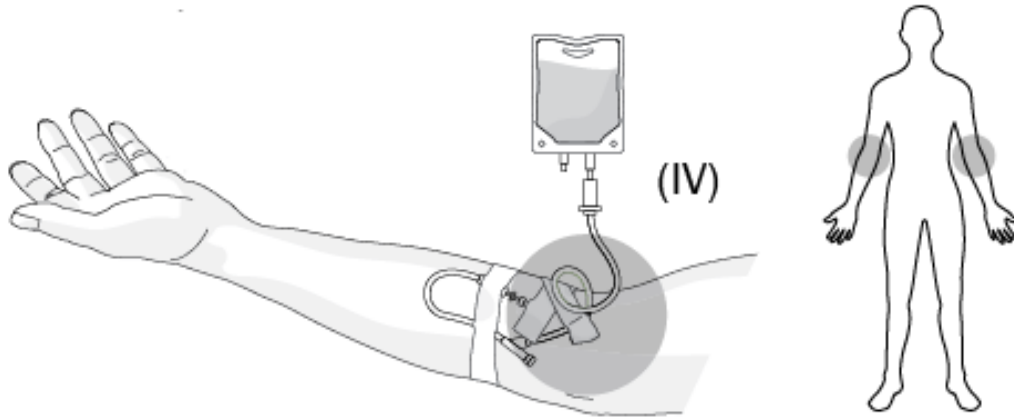
Clinic staff conducting consent discussion (print)	Clinic staff signature	Date	Time
--	------------------------	------	------

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
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*Witness is impartial and was present for the entire discussion of this consent form.

Appendix E Schematic of IV infusions



Appendix F Tables of procedures (for sample informed consent forms)

Groups 1 – 3

			Time after infusion									
Procedure	Screening visits)	Day 0	3 days	6 days	2 weeks	1 month	2 months	4 months	6 months	8 months	10 months	1 year
IV infusion		✓										
Medical history	✓											
Complete physical	✓											✓
Brief physical		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Urine test	✓				✓							
Blood drawn	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pregnancy test (participants assigned female sex at birth)*	✓	✓									✓	
HIV testing and pretest counseling**	✓							✓		✓		✓
Risk reduction counseling	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓
Interview/questionnaire(s)	✓	✓							✓			✓

* Persons who had a hysterectomy (removal of the uterus) or removal of both ovaries (verified by medical records), are not required to have a pregnancy test.'

** We will contact you with results of HIV testing.

Group 4

			Time after first infusion													
Procedure	Screening visit(s)	Day 0	3 days	6 days	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months	8 months	10 months	1 year	1 year & 2 months	1 year & 4 months
IV infusion		√							√							
Medical history	√															
Complete physical	√															√
Brief physical		√	√	√	√	√	√	√	√	√	√	√	√	√	√	
Urine test	√				√					√						
Blood drawn	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Pregnancy test (participants assigned female sex at birth)*	√	√							√						√	
HIV testing and pretest counseling**	√								√			√		√		√
Risk reduction counseling	√	√			√	√	√	√	√	√	√	√	√	√	√	√
Interview/questionnaire(s)	√	√							√		√			√		√

* Persons who had a hysterectomy (removal of the uterus) or removal of both ovaries (verified by medical records), are not required to have a pregnancy test.

** We will contact you with results of HIV testing.

Appendix G Laboratory procedures for Groups 1 – 3

Procedure	Ship to ¹	Assay location ²	Tube Type ⁴	Tube size (vol. capacity) ⁴	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
					Day:	Screening visit ³	D0	D3	D6	D14	D28	D56	D84	D112	D140	D168	D224	D280	D336	
					Week:		W0			W2	W4	W8	W12	W16	W20	W24	W32	W40	W48	
						Study Product Administration														
						PGT121 OR PGDM1400 OR 10-1074, + VRC07-523LS														
BLOOD COLLECTION																				
Screening/Diagnostic																				
Screening HIV test	Local lab	Local lab	EDTA	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
Syphilis ⁹	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics ⁷	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	—	—	—	—	10	—	—	10	—	20	40
Safety labs ¹⁰																				
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	—	5	—	5	—	—	5	—	5	5	5	5	45
Chemistry Panel ⁵	Local lab	Local lab	SST	5mL	5	5	—	—	5	—	5	—	—	5	—	5	5	5	5	45
Drug concentrations/detection																				
PGT121, PDGM1400, 10-1074, VRC07-523LS concentrations	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	y	y	y	y	y	y	—	y	—	y	y	y	y	0
Humoral assays																				
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	y	y	—	—	y	y	y	—	y	—	—	—	—	—	0
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL	—	y	y	—	—	y	y	y	—	y	—	—	—	—	—	0
Anti-Drug Antibody (ADA)																				
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	—	—	—	—	—	—	—	y	—	—	y	y	y	0
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	y	—	—	y	y	y	0
mAb Reaction ¹¹																				
Trypsase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL	—	See footnote 12			—	—	See footnote 12			—	See footnote 12	—	See footnote 12			0
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs / VITL	SST	8.5mL	—	See footnote y			—	—	—	—	—	—	—	—	—	—	—	0
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	See footnote y			—	—	—	—	—	—	—	—	—	—	—	0
STORAGE																				
Serum	CSR	—	SST	8.5mL	—	85 ¹⁴			42.5	42.5	42.5	43	42.5	—	42.5	—	42.5	42.5	42.5	510
Visit total					25	95			42.5	42.5	52.5	42.5	52.5	0	62.5	0	52.5	62.5	52.5	655
56-Day total ¹³					25	120			162.5	205	257.5	300	352.5	95	115	62.5	115	115	115	125
URINE COLLECTION ¹⁰																				
Urine dipstick ⁸	Local lab	Local lab			X	—	—	—	X	—	—	—	—	—	—	—	—	—	—	
Pregnancy test ⁶	Local lab	Local lab			X	X	—	—	—	—	—	—	—	—	—	—	—	X	—	

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 0 prior to study product administration.

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. Persons who have undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

⁷ At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 14 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).

⁸ And microscopy if needed.

⁹ Syphilis testing will be done by serology.

¹⁰ For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected.

¹¹ To investigate mAb reactions, assays may be performed on serum samples taken prior to the study product administration associated with the reaction and collected after the onset of reaction. Refer to the HVTN 130/HPTN 089 SSP for more information.

¹² SST blood will be collected at specific timepoints after the onset of any mAb reaction. Refer to the HVTN 130/HPTN 089 SSP for more information.

¹³ The 56-day blood total volume 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.

¹⁴ Of this volume, 17mL of SST blood will be collected 1 hour after the end of the infusion (see Section 9.3).

y = SST blood collected for serum storage will also cover specimen needs for drug concentrations, HIV-1 neutralizing Ab assays, non-neutralizing antiviral assays, and ADA detection and functional assays (including for any mAb reactions); no separate blood draw is needed.

Appendix H Laboratory procedures for Group 4

Procedure	Ship to ¹	Assay location ²	Tube Type ⁴	Tube size (vol. capacity) ⁴	Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Total
					Day:	Screening visit ³	D0	D3	D6	D14	D28	D56	D84	D112	D140	D168	D224	D280	D336	D392	D448	
					Week:		W0			W2	W4	W8	W12	W16	W20	W24	W32	W40	W48	W56	W64	
							Study Product Administration #1							Study Product Administration #2								
							PGDM1400 + PGT121 + VRC07-523LS							PGDM1400 + PGT121 + VRC07-523LS								
BLOOD COLLECTION																						
Screening/Diagnostic																						
Screening HIV test	Local lab	Local lab	EDTA	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HBsAg/anti-HCV	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
Syphilis ⁹	Local lab	Local lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics ⁷	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	—	—	—	—	10	—	—	10	—	10	—	20	50
Safety labs ¹⁰																						
CBC/ Differential	Local lab	Local lab	EDTA	5mL	5	5	—	—	5	—	5	5	5	5	5	5	5	5	5	5	5	65
Chemistry Panel ⁵	Local lab	Local lab	SST	5mL	5	5	—	—	5	—	5	5	5	5	5	5	5	5	5	5	5	65
Drug concentrations/detection																						
PGT121, PDGM1400, VRC07-523LS concentrations	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	y	0
Humoral assays																						
HIV-1 neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	y	y	—	—	y	y	—	y	y	y	y	—	—	—	—	—	0
Non-neutralizing antiviral assays	CSR	HVTN Labs	SST	8.5mL	—	y	y	—	—	y	y	—	y	y	y	y	—	—	—	—	—	0
Anti-Drug Antibody (ADA)																						
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs / VITL	SST	8.5mL	—	y	—	—	—	—	—	—	—	y	—	—	y	y	y	y	y	0
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	y	—	—	y	y	y	y	y	0
mAb Reaction ¹¹																						
Tryptase / C3 and C4 Complement / Cytokines	CSR	ARUP	SST	8.5mL	—	See footnote 12	—	—	See footnote 12													0
ADA detection assays (screening, confirmatory, titration)	CSR	HVTN Labs / VITL	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	See footnote y	—	—	—	—	—	—	—	0
ADA functional assay	CSR	HVTN Labs	SST	8.5mL	—	See footnote y	—	—	—	—	—	—	—	See footnote y	—	—	—	—	—	—	—	0
STORAGE																						
Serum	CSR	—	SST	8.5mL	—	85 ¹⁴	42.5	42.5	42.5	42.5	42.5	42.5	42.5	51 ¹⁴	42.5	42.5	42.5	42.5	42.5	42.5	42.5	688.5
Visit total					25	95	42.5	42.5	52.5	42.5	52.5	52.5	52.5	71	52.5	52.5	62.5	52.5	62.5	52.5	72.5	883.5
56-Day total ¹³					25	120	162.5	205	257.5	300	352.5	147.5	176	176	176	115	115	115	115	115	125	
URINE COLLECTION ¹⁰																						
Urine dipstick ⁸	Local lab	Local lab			X	—	—	—	X	—	—	—	—	—	X	—	—	—	—	—	—	
Pregnancy test ⁶	Local lab	Local lab			X	X	—	—	—	—	—	—	—	X	—	—	—	—	—	X	—	

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 0 prior to study product administration.
- 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. Persons who have undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.
- ⁷ At an early termination visit for a withdrawn or terminated participant who is not HIV-infected (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 16 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.12).
- ⁸ And microscopy if needed.
- ⁹ Syphilis testing will be done by serology.
- ¹⁰ For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis, and pregnancy tests will be collected.
- ¹¹ To investigate mAb reactions, assays may be performed on serum samples taken prior to the study product administration associated with the reaction and collected after the onset of reaction. Refer to the HVTN 130/HPTN 089 SSP for more information.
- ¹² SST blood will be collected at specific timepoints after the onset of any mAb reaction. Refer to the HVTN 130/HPTN 089 SSP for more information.
- ¹³ The 56-day total blood volume 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.
- ¹⁴ Of this volume, 17mL of SST blood will be collected 1 hour after the end of the infusion (see Section 9.3).
- y = SST blood collected for serum storage will also cover specimen needs for drug concentrations, HIV-1 neutralizing Ab assays, non-neutralizing antiviral assays, and ADA detection and functional assays (including for any mAb reactions); no separate blood draw is needed.

Appendix I Procedures at CRS for Groups 1 – 3

Visit	01 ¹	02 ²	03	04	05	06	07	08	09	10	11	12	13	14	Post
Day:		D0	D3	D6	D14	D28	D56		D112		D168	D224	D280	D336	
Week:		W0			W2	W4	W8		W16		W24	W32	W40	W48	
Procedure	Scr	Inf													
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, obtain demographics, randomize	X	—	—	—	—	—	—		—		—	—	—	—	—
Infusion															
Solicited AE assessment ³	—	X	—	—	—	—	—		—		—	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X		X		X	X	X	—	—
Risk reduction counseling ⁴	X	X	—	—	X	X	X		X		X	X	X	X	—
Contraception status assessment ⁵	X	X	—	—	X	X	X		X		X	X	X	X	—
Social impact assessment	—	X	—	—	—	—	X		X		X	X	X	X	
Behavioral risk assessment questionnaire ⁶	X	—	—	—	—	—	—		—		X	—	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—		—		X	—	—	X	—
Acceptability questionnaire	—	X	—	—	—	—	—		—		—	—	—	—	—
Concomitant medications	X	X	X	X	X	X	X		X		X	X	X	X	—
Intercurrent illness/Unsolicited AE assessment	—	X	X	X	X	X	X		X		X	X	X	X	—
HIV infection assessment ⁷	X	—	—	—	—	—	—		X		—	X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—		—		X	—	X	—	X
Sample Collection⁸															
	X	X	X	X	X	X	X		X		X	X	X	X	

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

² Specimens collected at Day 0 may be obtained within the 14 days prior to study product administration, except for a pregnancy test, which must be performed on urine or blood specimens within 24 hours prior to study product administration with negative results received prior to study product administration.

³ Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 130/HPTN 089 SSP).

⁴ Includes transmission risk reduction counseling for HIV-infected participants.

⁵ Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

⁶ Not applicable to HIV-infected participants.

⁷ Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. Not applicable for participants diagnosed with HIV infection.

⁸ For specimen collection requirements, see [Appendix G](#).

Appendix J Procedures at CRS for Group 4

Visit	01 ¹	02 ²	03	04	05	06	07	08	09 ³	10	11	12	13	14	15	16	Post
Day:		D0	D3	D6	D14	D28	D56	D84	D112	D140	D168	D224	D280	D336	D392	D448	
Week:		W0			W2	W4	W8	W12	W16	W20	W24	W32	W40	W48	W56	W64	
Procedure	Scr	Inf 1							Inf 2								
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, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Infusion⁴	—	X	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Solicited AE assessment ⁴	—	X	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Abbreviated physical exam	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Risk reduction counseling ⁵	X	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	—
Contraception status assessment ⁶	X	X	—	—	X	X	X	X	X	X	X	X	X	X	X	X	—
Social impact assessment	—	X	—	—	—	—	X	—	X	—	X	X	X	X	X	X	—
Behavioral risk assessment questionnaire ⁷	X	—	—	—	—	—	—	—	—	—	X	—	—	X	—	X	—
Social impact assessment questionnaire	—	—	—	—	—	—	—	—	—	—	X	—	—	X	—	X	—
Acceptability questionnaire	—	X	—	—	—	—	—	—	X	—	—	—	—	—	—	—	—
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
Intercurrent illness/Unsolicited adverse experience	—	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—
HIV infection assessment ⁸	X	—	—	—	—	—	—	—	X	—	—	X	—	X	—	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	—	—	X	—	—	X	—	X	—	X
Sample collection⁹	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	—

¹ Screening may occur over the course of several contacts/visits up to and including day 0 prior to study product administration.

² Specimens collected at Day 0 may be obtained within the 14 days prior to study product administration, except for a pregnancy test, which must be performed on urine or blood specimens within 24 hours prior to study product administration with negative results received prior to study product administration.

³ Blood draws required at study product administration visit must be performed prior to administration of study product; however, it is not necessary to have results prior to administration, except for results of a serum pregnancy test, if indicated. Lab tests may be drawn with the 3 days prior to study product administration.

⁴ Solicited AE assessments performed daily for at least 3 days following study product administration. CRS staff to contact participant to review and report Solicited AEs following the Solicited AE period (see the HVTN 130/HPTN 089 SSP).

⁵ Includes transmission risk reduction counseling for HIV-infected participants.

⁶ Contraception status assessment is required only for participants who were assigned female sex at birth and who are capable of becoming pregnant.

⁷ Not applicable to HIV-infected participants.

⁸ Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. Not applicable for participants diagnosed with HIV infection.

⁹ For specimen collection requirements, see [Appendix H](#).

Appendix K 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 L Protocol Signature Page

A phase 1 clinical trial to evaluate the safety, tolerability, pharmacokinetics, and antiviral activity of combinations of monoclonal antibodies PGT121, PGDM1400, 10-1074, and VRC07-523LS administered via intravenous infusion in 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

Investigator of Record Name (print)

Investigator of Record Signature

Date

DAIDS Protocol Number: HVTN 130/HPTN 089

DAIDS Protocol Version: Version 1.0

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