HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 122

A phase 1 double-blind, randomized clinical trial to evaluate the safety and immunogenicity of a recombinant oligomeric gp145 clade C Env protein (gp145 C.6980) in healthy, HIV-1–uninfected adult participants in the US

DAIDS DOCUMENT ID 12030

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CLINICAL TRIAL SPONSORED BY

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

STUDY PRODUCTS PROVIDED BY

Division of AIDS, NIAID, NIH
Bethesda, Maryland, USA
Vaccine Research Center
Frederick, Maryland, USA

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HVTN 122
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Contents

1 Ethical considerations

Multiple candidate HIV vaccines will need to be studied simultaneously in different populations around the world before a successful HIV preventive vaccine is found. 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) has addressed ethical concerns in the following ways:

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

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

- HVTN scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. Community Advisory Boards (CAB) are required by DAIDS and supported at all HVTN research sites to ensure community input.

- HVTN clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.

- Participants who become HIV infected during the trial are referred to medical practitioners to manage their HIV infection and to identify potential clinical trials they may want to join.

- The HVTN provides training so that all participating sites similarly ensure fair participant selection, protect the privacy of research participants, and obtain meaningful informed consent. During the study, participants will have their wellbeing monitored, and to the fullest extent possible, their privacy protected. Participants may withdraw from the study at any time.

- Prior to implementation, HVTN trials are rigorously reviewed by scientists who are not involved in the conduct of the trials under consideration.

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

- The HVTN designs its research to minimize risk and maximize benefit to both study participants and their local communities. For example, HVTN protocols provide enhancement of participants' knowledge of HIV and HIV prevention, as well as counseling, guidance, and assistance with any social impacts that may result from research participation. HVTN protocols also include careful medical review of each research participant's health conditions and reactions to study products while in the study.

- HVTN research aims to benefit local communities by directly addressing the health and HIV prevention needs of those communities and by strengthening the capacity of the communities through training, support, shared knowledge, and equipment. Researchers involved in HVTN trials are able to conduct other critical research in their local research settings.

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

2 IRB/EC review considerations

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

2.1 Minimized risks to participants

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

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants postvaccination and collecting information regarding side effects for several days postvaccination; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, vaccinations, 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.

2.2 Reasonable risk/benefit balance

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

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

2.3 Equitable participant selection

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

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

2.4 Appropriate informed consent

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

The protocol specifies that informed consent must be obtained before any study procedures are initiated and assessed throughout the trial (see Section 9.1). Each site is provided training in informed consent by the HVTN as part of its entering the HVTN. The HVTN requires a signed consent document for documentation, in addition to chart notes or a consent checklist.

2.5 Adequate safety monitoring

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

This protocol has extensive safety monitoring in place (see Section 10). Safety is monitored daily by HVTN Core and routinely by the HVTN 122 Protocol Safety Review Team (PSRT). In addition, the HVTN Safety Monitoring Board (SMB) periodically reviews study data.

2.6 Protect privacy/confidentiality

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

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

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

3 Overview

Title

A phase 1 double-blind, randomized clinical trial to evaluate the safety and immunogenicity of a recombinant oligomeric gp145 clade C Env protein (gp145 C.6980) in healthy, HIV-1–uninfected adult participants in the US

Primary objective(s)

To evaluate the safety and tolerability of 1 injection of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Secondary objectives

To evaluate the safety and tolerability of 3 injections of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

To characterize the immunogenicity of 1 injection of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

To characterize the immunogenicity of 3 injections of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Study products and routes of administration

- **gp145 C.6980**: gp145 C.6980 is an HIV-1 subtype C recombinant gp145 Env protein produced in CHO (Chinese hamster ovary) cells and derived from an acute Tanzanian clade C Env (C06980.v0.c22). gp145 C.6980 will be given with **aluminum hydroxide adjuvant**, mixed together at the clinical site. 300mcg (Group 1) and 100mcg (Group 2) of gp145 C.6980 will be admixed with **aluminum hydroxide adjuvant** containing ~600mcg ionic aluminum. The resulting vaccine/adjuvant mixtures will be given as single 1 mL intramuscular (IM) injections into the deltoid.

- **Placebo**: Sodium Chloride for Injection, 0.9% delivered as a 1 mL IM injection

Table 3-1 Schema

Study arm	Number	Dose	Month 0 (Day 0)	Month 2 (Day 56)	Month 6 (Day 168)
Group 1	25	300 mcg	gp145 C.6980 + alum	gp145 C.6980 + alum	gp145 C.6980 + alum
Group 2	15	100 mcg	gp145 C.6980 + alum	gp145 C.6980 + alum	gp145 C.6980 + alum
Group 3	5	NA	placebo	placebo	placebo
Total	45 (40/5)				

Note

Enrollment will proceed in all study arms simultaneously and will be restricted to a maximum of 1 participant per group per day until 20% of participants (ie, the first 9 participants [5 in Group 1, 3 in Group 2, and 1 in Group 3]) have been enrolled. The PSRT will review the safety and reactogenicity data reported for the first 2 weeks following the first vaccination for each of these participants and will determine whether it is safe to proceed with full enrollment.

Participants

45 healthy, HIV-1–uninfected volunteers aged 18 to 50 years: 40 vaccinees, 5 placebo recipients in the US

Design

Multicenter, randomized, placebo-controlled, double-blind trial

Duration per participant

12 months of scheduled clinic visits

Estimated total study duration

17 months (includes enrollment, planned safety hold, and follow-up)

Investigational New Drug (IND) sponsor

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

Study product providers

- **gp145 C.6980**: Division of AIDS, NIAID, NIH (Bethesda, Maryland, USA)
- **Aluminum hydroxide adjuvant**: Vaccine Research Center, NIAID, NIH (Frederick, Maryland, USA)

Core operations

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

Statistical and data management center (SDMC)

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

HIV diagnostic laboratory

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

Endpoint assay laboratories

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

Study sites

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

Safety monitoring

HVTN 122 PSRT; HVTN Safety Monitoring Board (SMB)

3.1 Protocol Team

Protocol leadership

Chair	Katharine Bar University of Pennsylvania 215-573-8497 bark@upenn.edu	*Statistician*	Yunda Huang SCHARP, FHCRC 206-667-5780 yunda@scharp.org
Cochair	Hong Van Tieu New York Blood Center 212-570-3081 htieu@nybloodcenter.org	*Medical officers*	Maggie Brewinski Isaacs DAIDS, NIAID 301-761-7009 maggie.brewinskiisaacs@nih.gov
Protocol Team leader	Shelly Karuna HVTN Core, FHCRC 206-667-4355 mkaruna@fredhutch.org	*Laboratory lead*	Mingchao Shen HVTN Laboratory Program 206-667-5360 mshen@fredhutch.org

Other contributors to the original protocol

Core medical monitor	Shelly Karuna HVTN Core, FHCRC	*Clinical safety specialist*	Megan Jones HVTN Core, FHCRC
Vaccine developer representative	Jane Halpern DAIDS, NIAID	*Clinical trials manager*	India Tindale HVTN Core, FHCRC
Laboratory protocol operations manager	On Ho HVTN Laboratory Program, FHCRC	*SDMC Associate director of lab science*	April Randhawa SCHARP, FHCRC
Regulatory affairs	Laurie Rinn HVTN Core, FHCRC	*SDMC Senior clinical data manager*	Gina Escamilla SCHARP, FHCRC
Clinic coordinator	Debbie Lucy New York Blood Center CRS	*DAIDS Project officer*	Michael Pensiero DAIDS, NIAID
Community Advisory Board (CAB) member	Aamina Morrison University of Pennsylvania CAB	*Protocol development managers*	Carter Bentley HVTN Core, FHCRC Ryan Jensen HVTN Core, FHCRC
DAIDS protocol pharmacist	Katherine Shin DAIDS, NIAID 240-627-3047	*Community engagement unit representative*	Stephaun Wallace HVTN Core, FHCRC
Statistical research associate	Mengshu Shao SCHARP, FHCRC	*Community educator/recruiter*	Jermaine McCrossin New York Blood Center CRS
Consultative investigator	Merlin Robb MHRP	*Technical editor*	Erik Schwab HVTN Core, FHCRC

4 Background

4.1 Vaccine product: gp145 C.6980 Env protein

The gp145 C.6980 protein was derived from a clade C strain isolated from an acutely infected Tanzanian individual (CO6980.v0.c22) [4]. A clade C founder virus was deemed advantageous as clade C infections represent more than half the HIV-1 pandemic and are prevalent in highly impacted regions, including southern and eastern Africa but also in other parts of the world [5,6]. Relative to sera from persons infected with other clades of HIV-1, sera from clade C–infected individuals have been shown to be more broadly cross-reactive, neutralizing the greatest number of viruses in multiclade neutralization panels [7-9]. Further, the use of a primary virus isolate obtained in acute infection may better represent the properties of transmitted/founder viruses, which are the target of preventive vaccines [10,11].

gp145 C.6980 is a novel immunogen constructed by modifying the gene for the CO6980.v0.c22 protein to terminate prior to the transmembrane region, thus retaining an intact membrane-proximal external region (MPER) without the carboxyl terminal cytoplasmic domain. Additional modifications to the gene were introduced to prevent cleavage at the gp120/gp41 cleavage site and to facilitate trimer assembly and antigen presentation. gp145 C.6980 is produced as a secreted protein from Chinese hamster ovary (CHO) cells and has been purified and tested in both *in vitro* and *in vivo* assays. The gp145 C.6980 immunogen was developed by the United States Military HIV Research Program (MHRP); the lot used in this study was manufactured by Avid Biosciences (Tustin, CA, USA). The study product for this trial is supplied by DAIDS.

The expressed and purified gp145 C.6980 was shown to be assembled in multiple forms, with a significant fraction represented as Env trimers (Figure 4-1A). Cryoelectron microscopy of the gp145 trimers demonstrate the expected “fan-blade” morphology (Figure 4-1B) [4].

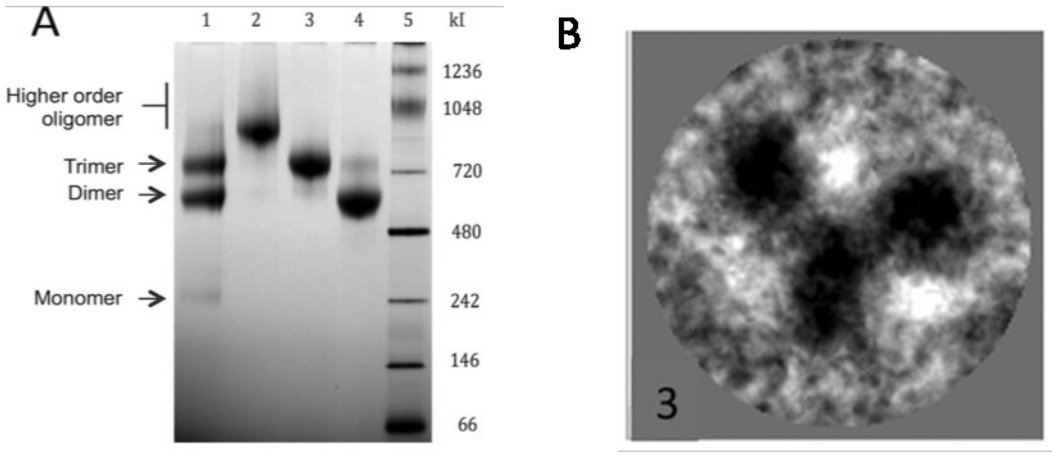

Figure 4-1 A fraction of gp145 C.6980 is expressed as trimeric Env. (A) Blue Native-PAGE analysis demonstrates that purified gp145 C.6980 exists in multiple oligomeric forms, including trimers. (B) The majority of the trimer fraction (lane 3) appears as true trimeric Envs with "fan-blade" morphology by cryoelectron microscopy [4].

The primary virus CO6940.v0.c22 displays epitopes of and is neutralized by broadly neutralizing antibodies (bnAbs) targeting MPER (4E10), the CD4 binding site (VRC01) and V2 glycans (PG9/PG16, PGT121); the trimeric gp145 C.6980 protein is similarly bound by each of these bnAbs and additional mAbs targeting V2 (697, 2158, 2297) [4]. Immunization of rabbits with each structural fraction was tested. All fractions of the gp145 C.6980 were immunogenic, with induced antibodies showing binding to clade C gp120 and gp140 Envs and cyclic V2 peptides as well as neutralization of Tier 1, and some Tier 2, viruses (Figure 4-2).

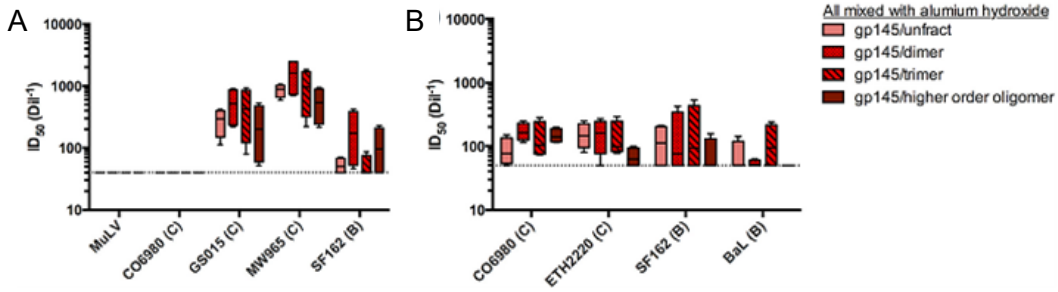

Figure 4-2 gp145 C.6980 is immunogenic in rabbits. Mean ID_{50} values for sera from rabbits vaccinated with gp145 fractions (unfractionated, dimers, trimers, higher order multimers) against clade B and C viruses in TZM-bl assay (A) or PBMC inhibition assay (B) [4].

Aluminum hydroxide (alum) will be used as an adjuvant, which will be co-administered with gp145 C.6980. When compared to 3 liposomal adjuvant formulations for immunogenicity in rabbits, alum was shown to generate comparable binding and neutralizing antibody titers [4].

For the study protocol, gp145 C.6980 produced in CHO cells will be given with alum as an adjuvant mixed together at the clinical site. Vaccinees will receive either 300 mcg (Group 1) or 100 mcg (Group 2) of gp145 C.6980 admixed with alum adjuvant containing ~600 mcg ionic aluminum. The resulting vaccine/adjuvant mixtures will be given as a single 1 mL IM injection in the

deltoid. Placebo recipients will receive sodium chloride 0.9% delivered as a 1 mL IM injection.

4.2 Rationale for trial concept

The development of a vaccine against HIV-1 infection remains a significant global health challenge. Based on the RV144 phase 3 HIV vaccine trial results, which provided the first clinical trial evidence that a vaccine combination could demonstrate modest efficacy in preventing HIV infection [12,13], an effective HIV vaccine is expected to require, as 1 component, an antigen that stimulates the production of an effective antibody response. This could consist of bnAbs that are capable of preventing HIV-1 entry into its target cells and blocking virus transmission [14,15] and/or non-neutralizing antibodies with effector functions [16]. Such an antigen is likely to be an Env glycoprotein, since this is the only protein expressed on the surface of the HIV virus particle that could serve as a target for vaccine-induced antibodies.

Vaccine candidates tested to date in humans have not yet successfully generated strong bnAb responses against a wide spectrum of viruses. However, the RV144 trial did demonstrate modest protection that was associated with antibody responses [17]. In RV144, a 31% decrease in risk of HIV infection was observed in participants who received ALVAC canarypox vector expressing Env, Gag, and Pro at 0, 1, 3, and 6 months and were boosted with a monomeric gp120 protein, AIDSVAX B/E, at 3 and 6 months, compared to those who received placebo. Subsequent analyses of immune responses have demonstrated that antibodies to the V1V2 region of HIV Env were inversely correlated with the risk of HIV-1 infection in vaccine recipients [18-20].

While the Env protein in AIDSVAX was a gp120 monomer, several lines of evidence suggest that a trimeric Env antigen may better expose quaternary epitopes and lead to an improved protective immune response against HIV-1 relative to monomeric protein [21-23]. In preclinical studies, the gp145 C.6980 protein has been demonstrated to elicit neutralizing antibodies to certain viruses or pseudoviruses in rabbits [4] (Section 4.6).

Hence, the goal of this trial is to evaluate the safety and immunogenicity of 2 dose levels of gp145 C.6980, a novel oligomeric Env antigen, in healthy, HIV-1–uninfected adult participants in the US and, if it is demonstrated to be safe and immunogenic, to qualify it for further clinical testing, most likely as 1 component in a combination vaccine prime-boost strategy.

4.3 Rationale for trial design

4.3.1 Dose (amount and number)

This study will test 2 doses: 300 mcg gp145 C.6980 with alum (n = 25) and 100 mcg gp145 C.6980 with alum (n = 15) compared to placebo (n = 5). The 300 mcg

dose is based on dosing of Env proteins used in RV144 [12]; the 100 mcg dose is being tested to explore immunogenicity of a lower dose regimen. The 2 doses are projected to be used in combination vaccine trials that may occur subsequently.

4.3.2 Schedule

All groups will receive the vaccine or placebo at Months 0, 2, and 6.

Enrollment will proceed in all groups simultaneously and will be restricted to a maximum of 1 participant per group per day until the initial 20%, or 9 participants (5 in Group 1, 3 in Group 2, and 1 in Group 3) have been enrolled and observed for 2 weeks. The PSRT will review safety data reported for the first 2 weeks following the first vaccination for each of these participants and will determine whether it is safe to proceed with full enrollment.

4.3.3 Choice of control

Placebo will be Sodium Chloride for Injection, 0.9% delivered as a 1 mL injection.

4.4 Plans for future product development and testing

This trial is a phase 1 double-blind, placebo-controlled randomized clinical trial to evaluate the safety and immunogenicity of a recombinant gp145 clade C Env protein in healthy, HIV-1–uninfected adult participants in the US. If the trial demonstrates that gp145 C.6980 is safe, tolerable, and immunogenic, it will be considered as an Env immunogen in subsequent combination vaccine trials. In particular, the developers of gp145 C.6980 have been in discussion with representatives from the China Centers for Disease Control regarding the prospect of evaluating this protein as a boost component in a regimen that includes a DNA prime and a recombinant Tiantan strain vaccinia vector boost [24,25].

4.5 Preclinical safety studies

gp145 C.6980 has not previously been tested in humans. The immunogenicity studies performed to date with the gp145 C.6980, as well as its physiochemical characterization, suggest that the protein retains the intended conformation predicted to be immunogenic and is not associated with any unexpected properties that would raise potential safety concerns. The safety of other HIV Env proteins administered with alum has been extensively studied in clinical trials and preclinical studies. The extensive clinical experience with these HIV Envs as vaccine antigens is described briefly below (Section 4.6.3).

4.6 Preclinical immunogenicity studies

Table 4-1 Summary of preclinical immunogenicity studies

Study number	Test Article	Adjuvant and Formulation	Animal	N	Dose	Route	Schedule	Assay
1	Unfractionated gp145 C.6980	$Al(OH)_3$ + gp145 C.6980	Rabbits	4	25mcg protein (+600 mcg alum)	IM	Week 0, 4, 8	Binding ELISA Neutralization by TZM-bl and PBMC
	Unfractionated gp145 C.6980	L(DMPG/MPLA) + gp145 C.6980						
	Unfractionated gp145 C.6980	L(DMPG/MPLA + gp145 C.6980)						
	Unfractionated gp145 C.6980	L(PIP/MPLA + gp145 C.6980)						
	None	L(DMPG/MPLA)						
2	Unfractionated gp145 C.6980	$Al(OH)_3$ + gp145 C.6980	Rabbits	4	25mcg protein (+600 mcg alum)	IM	Week 0, 4, 8	Binding ELISA Neutralization by TZM-bl and PBMC
	gp145 C.6980 dimer	$Al(OH)_3$ + gp145 C.6980						
	gp145 C.6980 trimer	$Al(OH)_3$ + gp145 C.6980						
	gp145 C.6980 multimer	$Al(OH)_3$ + gp145 C.6980						
	None	$Al(OH)_3$						

4.6.1 Immunogenicity of gp145 C.6980 in rabbits, study #1

The gp145 C.6980 protein has been evaluated in 2 rabbit studies testing the ability of the vaccine to stimulate a neutralizing antibody response (Table 4-1). Study 1 tested the ability of unfractionated gp145 C.6980 to stimulate binding and neutralizing antibody responses in rabbits. Unfractionated gp145 C.6980 with alum was tested against unfractionated gp145 C.6980 and liposomal adjuvants that were prepared to encapsulate (Groups 3 and 4) or mix with (Group 2) the test article. Animals were immunized at weeks 0, 4, and 8 via IM injection. Blood was collected at Weeks -2, 0, 4, 8, 10, and 12.

4.6.1.1 Binding antibody responses

Sera were collected 2 weeks after the last vaccination (Week 10) and tested for binding activity to homologous and heterologous Envs. Weak titers were seen in some animals to gp41 proteins, whereas there was a positive response against each of the clade C gp120 and gp140 proteins (Figure 4-3).

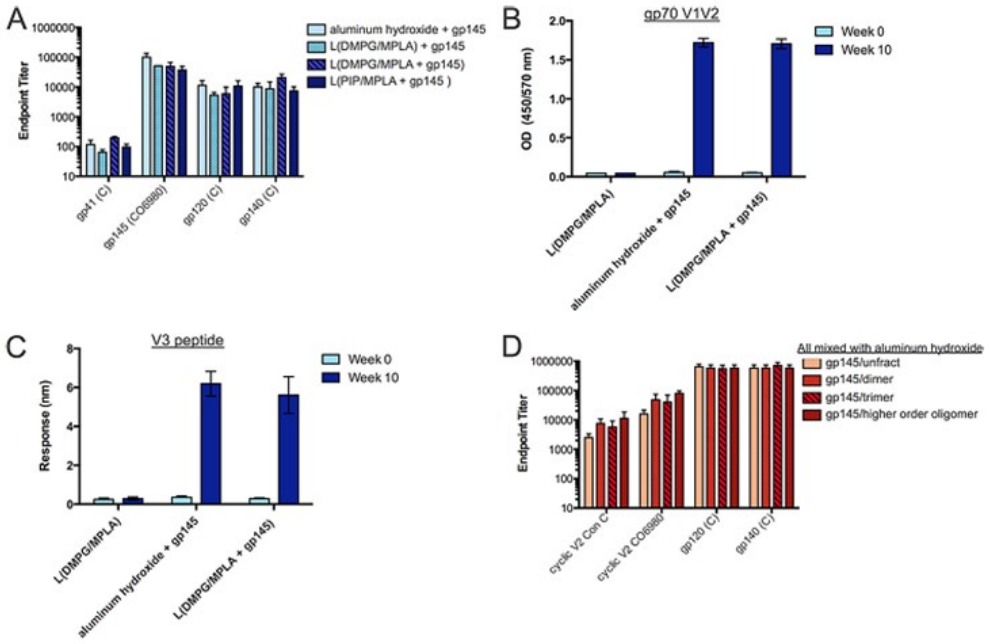

Figure 4-3 Fractionated and unfractionated gp145 C.6980 induced binding antibody responses in rabbits. Binding antibody titers elicited by vaccination with gp145 C.6980. Binding to various Env constructs by unfractionated gp145 C.6980–vaccinated rabbit sera in Study 1 (A). Binding of vaccinated animals' sera to V1V2 (B) and V3 (C) peptides. Binding responses were similar for unfractionated gp145 C.6980 and fractionated gp145 C.6980 (dimers, trimers, higher order oligomers) in Study 2 (D) [4].

4.6.1.2 Neutralizing antibody responses

Elicitation of neutralizing antibody responses was tested using the TZM-bl assay [26,27] and PBMC assay [28,29]. The TZM-bl assay provides a well-validated, high-throughput assessment of plasma inhibition of entry into a laboratory cell line. The PBMC neutralization provides a dose-response measure of plasma antibody inhibition of infectious molecular clones expressing luciferase reporters in a 72 hour culture of stimulated primary blood mononuclear cells. In the TZM-bl assay, sera from vaccinated rabbits neutralized 3 of 6 viruses, reflecting a predominantly Tier 1 (easy to neutralize) response. There was no neutralizing activity against the homologous CO6980 pseudovirus (Tier 2) or heterologous Tier 2 CRF01_AE viruses (Figure 4-4 A, C). In the PBMC assay, neutralization was seen against 5 tested viruses, including the homologous CO6980 strain (Figure 4-4 B, D).

4.6.2 Immunogenicity of gp145 C.6980 in rabbits, study #2: fractionated protein

In Study 2, rabbits were immunized with either unfractionated gp145 C.6980 or preparations enriched for dimers, trimers, or other higher order fractions based on size-exclusion chromatography (see Figure 4-1A). Sera were tested for binding and neutralizing antibody responses.

4.6.2.1 Binding antibody responses

Sera were collected 2 weeks after the last vaccination (week 10) and tested for binding activity to homologous and heterologous Envs (clade C gp120, subtype C gp140, and cyclic V2 peptides of the homologous CO6980.v0.c22 strain). Responses in sera from animals vaccinated with unfractionated gp145 C.6980 were similar to the responses seen in Study 1. Sera from animals vaccinated with purified fractions displayed similar profiles as the unfractionated animals in Study 1 and 2.

4.6.2.2 Neutralizing antibody responses

As in Study 1, elicitation of neutralizing antibody responses was tested in the TZM-bl assay and PBMC assay. Sera from vaccinated rabbits were tested against the 3 heterologous pseudoviruses that were neutralized in Study 1 and the homologous C.6980 pseudovirus. Neutralization activity was seen for the 3 heterologous Tier 1 viruses and was not different between the unfractionated and purified proteins. As in Study 1, neutralizing activity was seen against all 4 viruses in the PBMC assay. Thus, unfractionated and each oligomeric formulation elicited Tier 1 neutralizing antibody responses.

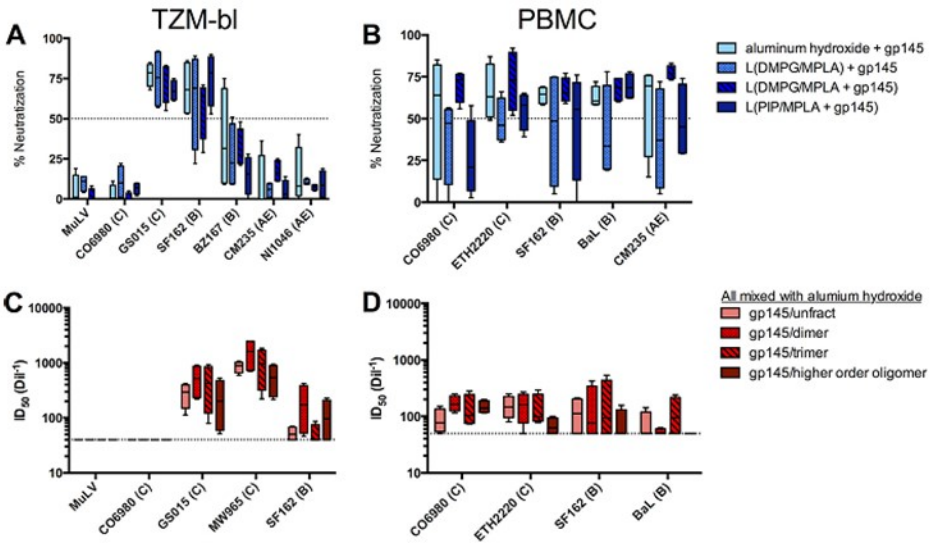

Figure 4-4 Fractionated and unfractionated gp145 C.6980 induce heterologous Tier 1 neutralizing antibody responses. Neutralizing antibody responses detected by TZM-bl (A and C) and PBMC assays (B and D). In Study 1, neutralization in TZM-bl assay is seen against Tier 1 viruses only in the TZM-bl assay (A) and more widely in the PBMC assay (B). In Study 2, similar titers are seen with fractionated and unfractionated gp145 C.6980 against Tier 1 viruses (C and D).

4.6.3 Preclinical study of gp145 C.6980 in non-human primates

gp145 C.6980 was administered to 16 Indian-origin rhesus macaques three times over a period of nine months in conjunction with recombinant live attenuated modified vaccinia Ankara (MVA) vector encoding HIV-1 GagPol/Env derived from subtypes A, C, and E. Animals received MVA at month 0, followed by

concurrent MVA and gp145 at months 3, 6, and 12. gp145 C.6980 immunizations consisted of 100 mcg of protein adjuvanted with aluminum hydroxide (Alhydrogel, Brenntag) delivered IM. The protein was safely administered and well-tolerated with no adverse events. Animal body weights and temperatures remained stable following each immunization.gp145 C.6980 was immunogenic in all animals, eliciting binding antibody responses with a median titer of 10^5 to gp140 (subtype C CN54) and $10^{3.7}$ to cyclic V2 peptide (gp145). Tier 1 neutralizing antibodies were also consistently observed, showing a median $ID50^{-1}$ of 10^3 to both MW965 and TH023 (subtype C and E, respectively). gp120-specific CD4+ T cells were observed in most animals, ranging from 0.1-0.5% of the memory compartment, while CD8+ T-cell responses were observed in only a subset of animals at 0.6-3% of memory cells. In sum, gp145 C.6980 showed consistent and robust immunogenicity with no safety concerns in nonhuman primates.

4.7 Clinical studies

Though gp145 C.6980 has not previously been evaluated in humans, the safety of other HIV Env proteins administered with alum has been extensively studied in clinical and preclinical studies. The extensive clinical experience with these HIV Envs as vaccine antigens is described briefly here.

Multiple monomeric Env proteins (gp120, gp140, gp145, gp160) have been administered in many clinical trials as the sole vaccine component or as a part of a prime boost regimen. The majority of proteins were produced in CHO cells (as is gp145 C.6980). Overall, vaccines consisting of or expressing HIV Env variants were well tolerated. The long-term safety data from NIAID-sponsored clinical trials conducted between 1987 and 2001 was analyzed by Gilbert and colleagues [30]. This report included 51 phase 1 and 2 trials, including data on 3189 uninfected participants; the majority of studies included an Env protein as an immunogen [30]. The published analysis concluded that 1 vaccine containing a C4-V3 polypeptide vaccine emulsified in incomplete Freund's adjuvant caused serious toxicity, but otherwise no serious safety problems were identified for any of the vaccines or adjuvants studied.

The largest clinical safety dataset for Env proteins is from the VAX003, VAX004, and RV144 studies, in which more than 12,000 participants received either AIDSVAX B/E or AIDSVAX B/B (each a mixture of 2 CHO-derived gp120 proteins totaling 600mcg [300mcg of each protein] in alum adjuvant). Safety data showed that these vaccines appeared safe and well tolerated [31]. In the RV144 trial, the frequency of reactions in AIDSVAX B/E recipients was 54.6% vs. 46.3% in placebo recipients. Pain and tenderness were the most frequent local reactions observed, and all reactions were generally mild and resolved within 3 days. Systemic reactogenicity was also observed more frequently in the combined vaccine group (77.2%) than the placebo group (59.8%). Systemic reactions following the third and fourth vaccination could not be attributed to a specific vaccine (ie, AIDSVAX or ALVAC).

Recent clinical experience with other oligomeric Env antigens is also available from a smaller number of studies. Oligomeric forms of gp140 clade C and clade B Env proteins manufactured by Novartis Vaccines and Diagnostics have been evaluated in 3 IND studies (clade C gp140 strain TV1 with MF59 and clade B gp140 strain SF162 with MF59) [32,33]. An oligomeric gp160 Env protein was administered to 45 participants in RV132, a phase 1-2 prime-boost study in Thailand [34]. More than 100 participants received the oligomeric subtype C product in a recent HVTN study (HVTN 086) [35]. The safety profile of these products was similar to that observed for the AIDSVAX products. The vaccines were generally well tolerated without vaccine-related serious adverse events.

4.8 Potential risks of study products and administration

Table 4-2 Summary of potential risks of study products and administration

Common	• Mild to moderate injection site pain, tenderness, erythema, or swelling/induration/edema • Malaise/fatigue, myalgia, or headache in the first few days following injection • A vaccine-induced positive HIV antibody test result
Less common	• Severe injection site pain or tenderness • Fever, chills, flu-like syndrome, arthralgia, rash, nausea, or dizziness in the first few days following injection • Vasovagal reaction/lightheadedness/dizziness related to the injection procedure • Transient changes in clinical laboratory values • Injection site hematoma, bruising/ecchymosis, other transient lesions, itching, or bleeding related to the injection procedure
Uncommon or rare	• Severe localized injection site reaction, such as sterile abscess or secondary bacterial infection • Allergic reaction, including rash, urticaria, angioedema, bronchospasm, or anaphylaxis • Muscle damage at the injection site
Theoretical risks	• Autoimmune disease • Effects on a participant's response to an approved HIV vaccine administered in the future • Effects on susceptibility to HIV, if the participant is exposed to HIV • Effects on the course of HIV infection/disease, if the participant is infected with HIV • Effects on the fetus and on pregnancy

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of 1 injection of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Primary endpoints 1:

Frequency of severe local and systemic reactogenicity signs and symptoms: pain, tenderness, maximum severity of pain and/or tenderness, erythema, induration, fever, malaise/fatigue, myalgia, headache, nausea, vomiting, chills, arthralgia, maximum severity of systemic symptoms (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

Frequency of AEs by treatment arm, by body system, Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and assessed relationship to study products (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

Serious adverse events (SAEs) throughout the active surveillance period

Laboratory measures of safety: white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, ALT, and creatinine at baseline and following vaccinations, by treatment arm (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

5.2 Secondary objectives and endpoints

Secondary objective 1:

To evaluate the safety and tolerability of 3 injections of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Secondary endpoints 1:

Frequency of severe local and systemic reactogenicity signs and symptoms: pain, tenderness, maximum severity of pain and/or tenderness, erythema, induration, fever, malaise/fatigue, myalgia, headache, nausea, vomiting, chills, arthralgia, maximum severity of systemic symptoms (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

Frequency of AEs by treatment arm, by body system, Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and assessed relationship to study products (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

SAEs throughout the active surveillance period

Laboratory measures of safety: white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, ALT, and creatinine at baseline and following vaccinations, by treatment arm (graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017)

Secondary objective 2:

To characterize the immunogenicity of 1 injection of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Secondary endpoints 2:

Response rates and levels of vaccine-induced binding antibodies to HIV proteins measured by the binding antibody multiplex assay (BAMA) at 2 weeks following the first vaccination

Secondary objective 3

To characterize the immunogenicity of 3 injections of gp145 C.6980 at 2 dose levels with alum adjuvant in HIV-seronegative low risk adults

Secondary endpoints 3:

Response rates and levels of vaccine-induced binding antibodies to HIV proteins measured by the BAMA at 2 weeks following the third vaccination

Response rates and levels of CD4+ and CD8+ T cells measured by intracellular cytokine staining (ICS) at 2 weeks following the third vaccination

Response rates and levels of neutralizing antibody responses against HIV-1 isolates at 2 weeks following the third vaccination

5.3 Exploratory objectives

Exploratory objective 1:

To describe participants' baseline characteristics (eg, previous exposure to vaccinia) and their impact on vaccine-induced immune responses

Exploratory objective 2:

To determine the frequency of circulating Tfh, Tfr, and plasmablasts in response to each vaccination regimen

Exploratory objective 3:

To further evaluate immunogenicity of each vaccine regimen, additional immunogenicity assays may be performed, including on samples from other timepoints, based on the HVTN Laboratory Assay Algorithm.

Exploratory objective 4:

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

6 Statistical considerations

6.1 Accrual and sample size calculations

Recruitment will target enrolling 45 healthy, HIV-uninfected adult participants aged 18 to 50 years, at low risk for HIV infection: 40 vaccine and 5 placebo recipients. Each participant will be randomly assigned to receive 1 of 2 doses of the vaccine regimen or placebo in a 5:3:1 ratio with 25, 15, and 5 participants in the 300 mcg dose (Group 1), 100 mcg dose (Group 2) and placebo (Group 3) arms, respectively. Since the 300 mcg dose level will be considered in future China CDC/NIAID/HVTN collaborative trials, the sample size of Group 1 accounts for the minimal sample size requirement (≥ 20) by China FDA to generate safety data for exporting the vaccine to China. The placebo arm provides a control group for assay quality assurance and blinding.

To ensure that both men and women will be adequately represented in the trial, the trial will enroll at least approximately 40% of each sex assigned at birth overall. Hence, when approximately 18 participants of 1 sex are enrolled, sites will be notified to stop further recruitment of persons of that sex assigned at birth.

Since enrollment is concurrent with receiving the first study vaccination, all participants will provide some safety data. However, for immunogenicity analyses, it is possible that data may be missing for various reasons, such as participants terminating from the study early, problems in shipping specimens, low cell viability of processed PBMCs, or high assay background levels. 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 10% is a reasonable estimate for the rate of missing data at days 14 and 182. For this reason, the sample size calculations in Section 6.1.2 account for 4 enrolled participants having missing data for the primary immunogenicity endpoint.

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 vaccine arm of the study (n = 15, 25), there is a 90% chance of observing at least 1 event if the true rate of such an event is 14.3% or 8.9% or more, respectively; and there is a 90% chance of observing no events if the true rate is 0.4% or 0.7% less, respectively. For vaccine arms combined (n = 40), there is a 90% chance of observing at least 1 event if the true rate of such an event is 5.6% or more; and there is a 90% chance of observing no events if the true rate is 0.26% or less. As a reference, in previous AVEG HIV vaccine trials, 3.5% of control participants experienced an SAE; in HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE.

Probabilities of observing 0 and 2 or more events among 15, 25, or 40 vaccine recipients are presented in Table 6-1 below for a range of possible true AE rates. These calculations provide a complete picture of the sensitivity of this study design to identify potential safety problems with the vaccine. For example, we see that if the true rate of AEs is 1%, there is an 86%, 78%, or 67% chance that no events will be observed in the vaccine arm of 15, 25, or 40 participants, respectively.

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among n=15, 25 or 40 vaccine recipients, for different true event rates

True event rate (%)	Pr(0/15)	Pr(2+/15)	Pr(0/25)	Pr(2+/25)	Pr(0/40)	Pr(2+/40)
1	0.860	0.010	0.778	0.026	0.669	0.061
3.5	0.586	0.095	0.410	0.218	0.240	0.411
5	0.463	0.171	0.277	0.358	0.129	0.601
10	0.206	0.451	0.072	0.729	0.015	0.920
20	0.035	0.833	0.004	0.973	<0.001	0.999
30	0.005	0.965	<0.001	0.998	<0.001	>0.999
40	<0.001	0.995	<0.001	>0.999	<0.001	<0.999

An alternative way of describing the statistical properties of the study design is in terms of the 95% confidence interval (CI) for the true rate of an AE based on the observed data. Table 6-2 shows the 2-sided 95% CIs for the probability of an event based on a particular observed rate. Calculations are done using the score test method [36]. If none of the 15, 25 or 40 vaccine recipients experience a safety event, the 95% 2-sided upper confidence bound for the true rate of such events is 21.8%, 13.7% or 8.81%, respectively.

Table 6-2 Two-sided 95% confidence intervals based on observing a particular rate of safety endpoints for arms of size n_1 and n_2

Observed event rate	CI (%)
0/15	(0.00, 21.8)
1/15	(0.17, 31.9)
2/15	(1.66, 40.5)
0/25	(0.00, 13.7)
1/25	(0.10, 20.4)
2/25	(0.98, 26.0)
0/40	(0.00, 8.81)
1/40	(0.06, 13.2)
2/40	(0.61, 16.9)

6.1.2 Sample size calculations for immunogenicity

The main goals of this trial regarding immunogenicity outcomes involve a preliminary estimation of response rates based on data from the BAMA, ICS, and nAb assays among vaccinees at 2 weeks following vaccination. No adjustment for multiple comparisons will be made for the use of multiple assays. The precision with which the true response rate can be estimated from the observed data depends on the true underlying response rate and the sample size. Two-sided 95%

confidence intervals for the response rate based on observing a particular rate of responses in the vaccinees is shown in Table 6-3. Calculations are done using the score test method [36]. The n = 13, 22, 36 assumes a 10% rate of missing immunogenicity data.

Table 6-3 Two-sided 95% confidence intervals for the true response rate based on observing a particular rate of responses in the vaccinees (n = 13, 22, 36)

No. of responses	Observed response rate (%)	CI
	n = 13	
3/13	23.1	[8.2, 50.2]
5/13	38.5	[17.7, 64.5]
7/13	53.8	[29.1, 76.8]
11/13	84.6	[57.8, 95.7]
12/13	92.3	[66.7, 98.6]
	n = 22	
3/22	13.6	[4.8, 33.3]
5/22	22.7	[10.1, 43.4]
7/22	31.8	[16.4, 52.7]
11/22	50.0	[30.7, 69.3]
15/22	68.2	[47.3, 83.6]
19/22	86.4	[66.7, 95.3]
20/22	90.9	[72.2, 97.5]
	n = 36	
3/36	8.3	[2.9, 21.8]
5/36	13.9	[6.1, 28.7]
7/36	19.4	[9.8, 35]
11/36	30.6	[18, 46.9]
15/36	41.7	[27.1, 57.8]
19/36	52.8	[37, 68]
23/36	63.9	[47.6, 77.5]
27/36	75	[58.9, 86.2]
33/36	91.7	[78.2, 97.1]

6.2 Randomization

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

6.3 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments (eg, vaccine or control). Study product assignments are accessible to those HVTN CRS pharmacists, DAIDS protocol pharmacists and contract monitors, and SDMC staff who are required to know

this information in order to ensure proper trial conduct. Any discussion of study product assignment between pharmacy staff and any other HVTN CRS staff is prohibited. The HVTN SMB members also are unblinded to treatment assignment in order to conduct review of trial safety.

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

Emergency unblinding decisions will be made by the site investigator. If time permits, the HVTN 122 PSRT should be consulted before emergency unblinding occurs. See the HVTN MOP for more information.

6.4 Statistical analyses

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

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

No formal multiple comparison adjustments will be employed for multiple safety endpoints, multiple primary immunogenicity endpoints, or secondary endpoints. However, multiplicity adjustments will be made for certain immunogenicity assays, as discussed below, when the assay endpoint is viewed as a collection of hypotheses (eg, testing multiple peptide pools to determine a positive response).

6.4.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and immunogenicity 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 vaccination, all participants will have received at least 1 vaccination and therefore will provide some safety data.

6.4.3.1 Reactogenicity

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

6.4.3.2 AEs and SAEs

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

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last vaccination, and number of vaccinations 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 (section 9.8) will be tabulated by treatment arm for each postvaccination 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 vaccination discontinuation and early study termination

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

6.4.4 Immunogenicity analysis

6.4.4.1 General approach

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

Discrete categorical assay endpoints (eg, response rates) will be analyzed by tabulating the frequency of positive response for each assay by antigen and treatment arm at each timepoint for which an assessment is performed. Crude response rates will be presented with their corresponding 95% confidence interval estimates calculated using the score test method [36]. Because of the small numbers of control participants, no adjustment will be made to the vaccine arm estimates for the false positive rates in the control arms. Barnard or Fisher's exact tests, as specified in the SAP, will be used to compare the response rates of the 2 vaccine arms, with a significant difference declared if the 2-sided p-value is $\leq$ 0.05. In general Barnard's is preferred since under most circumstances it is more powerful than Fisher's [37].

For quantitative assay data (eg, IgG binding Ab response from the multiplex assay or CD4+/CD8+ T cell response from the ICS assay), graphical and tabular summaries of the distributions by antigen, treatment arm, and timepoint will be made. For all primary and secondary immunogenicity endpoints, box plots and plots of estimated reverse cumulative distribution curves will be used for graphical display of all of the study arms. Typically the results will be shown for each vaccine arm and for the control arm separately.

The difference between arms at a specific timepoint may be tested with a nonparametric Wilcoxon rank sum test if the data are not normally distributed and with a 2-sample t-test if the data appear to be normally distributed. An appropriate data transformation (eg, $\log_{10}$ transformation) may be applied to better satisfy assumptions of symmetry and homoscedasticity (constant variance).

6.4.4.2 Multivariate display of immunogenicity endpoints

Data visualization techniques may be used to explore the relationship among immunogenicity readouts. The set of readouts may be based on 1 of the primary endpoints (eg, ICS), on the set of primary endpoints, or on immunogenicity endpoints that also include secondary or exploratory endpoints. To understand the relationship between pairs of readouts, scatter plots may be used when the number of readouts is small or for a larger number of readouts, a heat map showing the degree of correlation between any 2 pairs. Principal component analysis (PCA) and associated "biplots" of the scores and loadings are particularly useful to understand associations between readouts, especially when readouts are correlated [38]. PCA is a method to reduce the dimensionality of the number of readouts to a smaller set of values (principal components) that are normalized linear combinations of the readouts in such a way that the first principal component accounts for the most variability in the data and subsequent components, while maximizing variability, are uncorrelated with each other. A 'biplot' displays the first and second principal component scores and principal component loadings. The x-axis is the value from the first principal component and the y-axis is the second principal component, where each axis label includes the percentage of variation in the total set of readouts captured by the principal component. The top axis is the first principal component loadings and the right axis is the second principal component loadings. An arrow is drawn for each immunogenicity readout (eg, Env-specific CD4+ T cell polyfunctionality score, Env-specific CD8+ T cell total magnitude) from the origin to the point defined by its first 2 principal component loadings. The length of the arrow represents the amount of total variation of the set of readouts captured by the given readout. The direction of an arrow conveys the extent to which the variation of a readout is in the direction of the first or second principal component. The angle between 2 arrows conveys information about the correlation of the 2 readouts, with a 0 degree angle denoting perfect correlation and a 90 degree angle denoting no correlation. Each arrow on the biplot is labeled by the immunogenicity readout it represents. A biplot is annotated with key meta-information such as the treatment arm (most common application) or a demographic category. Depending on the application, K-means clustering and hierarchical clustering may also be applied for multivariate graphical display of immunogenicity readouts.

6.4.4.3 Secondary analysis of binding antibody data as measured by the BAMA assay

When a small panel of antigens (eg, ≤ 5) is being assessed in a multiplexed immunoassay, the response magnitudes and rates at 2 weeks following the first and third vaccinations will be evaluated for each antigen. When a larger panel is being assessed, in addition to assessing each antigen separately, a summary measure across a group of similar antigens will be calculated, for example, a weighted-average may be constructed to account for the correlations between antigens as an integrated magnitude of responses to multiple antigens. Then this summary measure may be used as the outcome variable to assess if this overall response measure differs by arms.

6.4.4.4 Secondary analysis of CD4+ and CD8+ T-cell response as measured by the ICS assay

The analysis of CD4+ and CD8+ T-cell response rates as measured by the ICS assay will be evaluated and compared as described under the general approach. For each T-cell subset, the positivity call for each peptide pool will include a multiple comparison adjustment for the number of peptide pools used in the assay. In general, the Mixture Models for Single-cell Assays (MIMOSA) statistical framework [39] and/or the Fisher's exact test-based positivity criteria will be used. Details of the positivity criteria will be discussed in the SAP. The magnitude of marginal response will be analyzed as described for quantitative data in the general approach section. For each T-cell subset, graphs will be used to display the background-subtracted magnitudes for each participant by protein, treatment arm, and timepoint. When 3 or more cytokines are being measured by the ICS assay, the polyfunctionality of ICS responses may also be analyzed as an exploratory endpoint. Besides descriptive plots of the magnitude of polyfunctional responses, the Combinatorial Polyfunctionality analysis of Antigen-Specific T-cell Subsets () statistical framework [40] may also be used to perform joint modelling of multiple T-cell subsets of different cytokine combinations. For example, the functionality score (FS) and the polyfunctionality score (PFS) may be used to summarize the multi-parameter ICS responses.

6.4.5 Analyses prior to end of scheduled follow-up visits

Any analyses conducted prior to the end of the scheduled follow-up visits should not compromise the integrity of the trial in terms of participant retention or safety or immunogenicity endpoint assessments. In particular, early unblinded analyses by treatment assignment require careful consideration and should be made available on a need to know basis only.

6.4.5.1 Safety

During the course of the trial, unblinded 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 122 PSRT. The HVTN leadership must approve any other requests for unblinded safety data prior to the end of the scheduled follow-up visits.

6.4.5.2 Immunogenicity

An unblinded statistical analysis by treatment assignment of a primary immunogenicity endpoint may be performed when all participants have completed the corresponding primary immunogenicity visit and data are available for analysis from at least 80% of these participants. Similarly, an unblinded statistical analysis by treatment assignment of a secondary or exploratory immunogenicity endpoint may be performed when all participants have completed the corresponding immunogenicity visit and data are available for analysis from at least 80% of these participants. However, such analyses for a secondary or exploratory immunogenicity endpoint will only take place after at

least 1 of the primary immunogenicity endpoints of the same class (humoral or cell-mediated) or, if no primary endpoint of the same class, at least 1 of the primary immunogenicity endpoints reaches the aforementioned threshold. The Laboratory Program will review the analysis report prior to distribution to the protocol chairs, DAIDS, vaccine developer, and other key HVTN members and investigators. Distribution of reports will be limited to those with a need to know for the purpose of informing future trial-related decisions. The HVTN leadership must approve any other requests for HVTN immunogenicity analyses prior to the end of the scheduled follow-up visits.

7 Selection and withdrawal of participants

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

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

Determination of eligibility, taking into account all inclusion and exclusion criteria, must be made within 56 days prior to enrollment unless otherwise noted in Sections 7.1 and 7.2.

7.1 Inclusion criteria

General and Demographic Criteria

1. **Age** of 18 to 50 years

2. **Access to a participating HVTN CRS** and willingness to be followed for the planned duration of the study

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

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

5. **Agrees not to enroll in another study** of an investigational research agent before the last scheduled 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. Low risk guidelines are found on the protocol web page under Study Materials on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn122).

Laboratory Inclusion Values

Hemogram/CBC

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

11. **White blood cell count** = 3,300 to 12,000 cells/mm^3

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

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

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

Chemistry

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

Virology

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

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

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

Urine

19. **Normal urine**:

    - Negative urine glucose, and
    - Negative or trace urine protein, and

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

Reproductive Status

20. **Volunteers who were born female**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test performed prior to vaccination on the day of initial vaccination. 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.

21. **Reproductive status**: A volunteer who was born female must:

    - Agree to consistently use effective contraception (see Appendix A) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment until after the last required protocol clinic visit. Effective contraception is defined as using the following methods:
        - Condoms (male or female) with or without a spermicide,
        - Diaphragm or cervical cap with spermicide,
        - Intrauterine device (IUD),
        - Hormonal contraception, or
        - Any other contraceptive method approved by the HVTN 122 PSRT
        - Successful vasectomy in the male partner (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy);
    - Or not be of reproductive potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation;
    - Or be sexually abstinent.

22. **Volunteers who were born female must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

7.2 Exclusion criteria

General

1. **Blood products** received within 120 days before first vaccination

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

3. **Body mass index (BMI)** ≥ 40; or BMI ≥ 35 with 2 or more of the following: age > 45, systolic blood pressure > 140 mm Hg, diastolic blood pressure > 90 mm Hg, current smoker, known hyperlipidemia

4. **Intent to participate in another study** of an investigational research agent or any other study that requires non-HVTN HIV antibody testing during the planned duration of the HVTN 122 study

5. **Pregnant or breastfeeding**

6. **Active duty and reserve US military personnel**

Vaccines and other Injections

7. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 122 PSRT will determine eligibility on a case-by-case basis.

8. **Non-HIV experimental vaccine(s) received within the last 5 years** in a prior vaccine trial. Exceptions may be made by the HVTN 122 PSRT for vaccines that have subsequently undergone licensure by the FDA. For volunteers who have received control/placebo in an experimental vaccine trial, the HVTN 122 PSRT will determine eligibility on a case-by-case basis. For volunteers who have received an experimental vaccine(s) greater than 5 years ago, eligibility for enrollment will be determined by the HVTN 122 PSRT on a case-by-case basis.

9. **Live attenuated vaccines** other than influenza vaccine received within 30 days before or scheduled and intended to be received within 14 days after the first vaccination (eg, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever)

10. **Influenza vaccine or any vaccines that are not live attenuated vaccines** and were received within 14 days prior to first vaccination (eg, tetanus, pneumococcal, Hepatitis A or B)

11. **Allergy treatment with antigen injections** within 30 days before first vaccination or that are scheduled and intended to be received within 14 days after first vaccination

Immune System

12. **Immunosuppressive medications** received within 168 days before first vaccination. (Not exclusionary: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatitis; or [4] a single course of prednisone or equivalent at doses < 60 mg/day and length of therapy < 11 days with completion at least 30 days prior to enrollment.)

13. **Serious adverse reactions to vaccines or to vaccine components,** including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain. (Not excluded from participation: a volunteer who had a nonanaphylactic adverse reaction to pertussis vaccine as a child.)

14. **Immunoglobulin** received within 60 days before first vaccination

15. **Autoimmune disease**

16. **Immunodeficiency**

Clinically significant medical conditions

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

18. **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 injections or blood draws,
    - A condition that requires active medical intervention or monitoring to avert grave danger to the volunteer's health or well-being during the study period,
    - A condition or process for which signs or symptoms could be confused with reactions to vaccine, or
    - Any condition specifically listed among the exclusion criteria below.

19. **Any medical, psychiatric, occupational, or other condition** that, in the judgment of the investigator, would interfere with, or serve as a contraindication to, protocol adherence, assessment of safety or reactogenicity, or a volunteer's ability to give informed consent

20. **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.

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

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

Exclude a volunteer who:

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

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

24. **Thyroidectomy, or thyroid disease** requiring medication during the last 12 months

25. **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.

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

27. **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)

28. **Seizure disorder:** History of seizure(s) within past 3 years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.

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

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

7.3 Participant departure from vaccination schedule or withdrawal

This section concerns an individual participant's departure from the vaccination schedule. Pause rules for the trial as a whole are described in Section 11.4.

7.3.1 Delaying vaccinations for a participant

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

- Within 45 days prior to any study injection
  - Receipt of blood products or immunoglobulin
- Within 30 days prior to any study injection
  - Receipt of live attenuated vaccines other than influenza vaccine
  - Receipt of allergy treatment with antigen injections
- Within 14 days prior to any study injection
  - Receipt of influenza vaccine or any vaccines that are not live attenuated vaccines (eg, pneumococcal)
- Pre-vaccination abnormal vital signs or clinical symptoms that may mask assessment of vaccine reaction.

Vaccinations should not be administered outside the visit window period specified in the HVTN 122 Study Specific Procedures.

In order to avoid vaccination delays and missed vaccinations, participants who plan to receive licensed vaccines or allergy treatments should be counseled to schedule receipt of these substances, when possible, outside the intervals indicated above. The effects of these substances on safety and immunogenicity assessments and their interactions with study vaccines are unknown. Therefore, if circumstances allow, these substances should also be avoided in the 2 week interval between a study vaccination and completion of the 2 week postvaccination follow-up visit.

7.3.2 Participant departure from vaccination schedule

Every effort should be made to follow the vaccination schedule per the protocol. If a participant misses a vaccination and the visit window period for the vaccination has passed, that vaccination cannot be given. The participant should be asked to continue study visits. The participant should resume the vaccination

schedule with the next vaccination unless there are circumstances that require further delay or permanent discontinuation of vaccination (see Sections 7.3.1 and 7.3.3).

7.3.3 Discontinuing vaccination for a participant

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

- Co-enrollment in a study with an investigational research agent (rare exceptions allowing for the continuation of vaccinations may be granted with the unanimous consent of the HVTN 122 PSRT).

- Clinically significant condition (ie, a condition that affects the immune system or for which continued vaccinations and/or blood draws may pose additional risk), including but not limited to the following:
  - Pregnancy (regardless of outcome)
  - Any grade 4 local or systemic reactogenicity symptom, lab abnormality, or AE that is subsequently considered to be related to vaccination
  - Any grade 3 lab abnormality or other clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to vaccination; upon review, the HVTN 122 PSRT may allow continuation of vaccination if a participant had grade 3 erythema and/or induration
  - SAE that is subsequently considered to be related to vaccination
  - Clinically significant type 1 hypersensitivity reaction associated with study vaccination. Consultation with the HVTN 122 PSRT is required prior to subsequent vaccinations following any type 1 hypersensitivity reaction associated with study vaccination

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

Such participants should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated.

In addition, vaccinations will be stopped for participants diagnosed with HIV infection. HIV-infected participants will not continue in the trial (see Sections 7.3.4 and 9.5.1).

7.3.4 Participant termination from the study

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

- Participant refuses further participation,
- Participant relocates and remote follow-up or transfer to another HVTN CRS is not possible,
- HVTN CRS determines that the participant is lost to follow-up,
- Participant becomes HIV infected,
- 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 Table 3-1. See the Investigator's Brochures (IB) for further information about study products.

8.1 Vaccine regimen

The schedule of vaccination is shown in Section 3 and additional information is given below.

Group 1

Treatment 1 (T1): gp145 C.6980, 300 mcg, admixed with Aluminum Hydroxide Suspension to be administered as 1 mL IM in the deltoid at Months 0, 2, and 6

Group 2

Treatment 2 (T2): gp145 C.6980, 100 mcg, admixed with Aluminum Hydroxide Suspension to be administered as 1 mL IM in the deltoid at Months 0, 2, and 6

Group 3

Placebo 3 (P3): Placebo for gp145 C.6980 (Sodium Chloride for Injection, 0.9%) to be administered as 1 mL IM in the deltoid at months 0, 2, and 6

8.2 Study product formulation

gp145 C.6980 [labeled as HIV Env gp145 C.6980]:

The gp145 C.6980 protein will be provided as 600 mcg per mL clear colorless to slightly yellow solution when thawed. Each single-use vial contains 0.5 mL (300 mcg) of product. The vials will have a nominal fill volume sufficient to allow withdrawal of 0.5 mL. The product must be stored frozen at -65°C or colder.

The study product is described in further detail in the Investigator's Brochure (IB).

Placebo for gp145 C.6980 (Sodium Chloride for Injection, 0.9%):

Sodium Chloride for Injection, 0.9% will be used as the placebo for gp145 C.6980. The product must be stored as directed by the manufacturer.

Aluminum Hydroxide Suspension [labeled as Aluminum Hydroxide Suspension]:

The Aluminum Hydroxide Suspension appears as an opaque, white gelatinous precipitate in aqueous suspension. The product is provided in 3 mL size vial containing 0.7 mL (3.5 mg of aluminum) per vial. The Aluminum Hydroxide Suspension was vialed by Leidos Biomedical Research, Inc., Frederick, Maryland, for the NIH Vaccine Research Center, utilizing Alhydrogel '85' 2%, an aluminum hydroxide wet gel suspension from Brenntag Biosector (Denmark), a well-known source for quality GMP materials, diluted to a concentration of 5 mg/mL aluminum content with water for injection and vialed under aseptic conditions compliant with cGMP regulations. The product must be stored refrigerated at 2° to 8° C.

8.3 Preparation of study products

Pharmacists should refer to 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. At minimum, study products must be prepared in a biological safety cabinet or an isolator by appropriately trained and qualified pharmacy personnel using aseptic technique.

8.3.1 gp145 C.6980, 300 mcg, admixed with Aluminum Hydroxide Suspension (Group 1)

One vial of gp145 C.6980, 1 vial of Aluminum Hydroxide Suspension, 1 vial/ampule of Sterile Water for Injection, and 1 empty sterilized vial will be needed to prepare the dose.

Prior to dispensing, the pharmacist will retrieve the gp145 C.6980 vial from the freezer and allow to thaw at room temperature. The pharmacist will also retrieve the Aluminum Hydroxide Suspension vial from the refrigerator. The pharmacist will retrieve Sterile Water for Injection vial and empty sterilize vial from storage.

Using aseptic technique, the pharmacist will gently swirl the contents of the vial containing aluminum hydroxide, withdraw 0.12 mL of the aluminum hydroxide and inject it into the empty sterilize vial (mixing vial). The pharmacist will then add 0.38 mL of Sterile Water for Injection to the mixing vial which contains 0.12 mL of aluminum hydroxide. The mixing vial should be gently swirled and inverted (do not shake). Next, the pharmacist will then gently swirl the vial containing gp145 C.6980 after which, using aseptic technique, the pharmacist will withdraw 0.5 mL (300 mcg) of gp145 C.6980 from the correct vial and inject it into the mixing vial (which contains aluminum hydroxide mixed with Sterile Water for Injection). After gentle swirling and inversion (do not shake vigorously) the pharmacist, using aseptic technique, will withdraw 1 mL of the mixed preparation for dosing into a 2, 3, or 5 mL size syringe. The pharmacist will apply an overlay to the syringe.

The syringe should be labeled as "HVTN 122 study product". The syringe must also be labeled for administration in the deltoid and "Gently roll the syringe prior

to administration". This study product should be administered as soon as possible after preparation.

8.3.2 gp145 C.6980, 100 mcg, admixed with Aluminum Hydroxide Suspension (Group 2)

One vial of gp145 C.6980, 1 vial of Aluminum Hydroxide Suspension, 1 vial/ampule of Sterile Water for Injection, and 1 empty sterilized vial will be needed to prepare the dose.

Prior to dispensing, the pharmacist will retrieve the gp145 C.6980 vial from the freezer and allow to thaw at room temperature. The pharmacist will also retrieve the Aluminum Hydroxide Suspension vial from the refrigerator. The pharmacist will retrieve Sterile Water for Injection vial and empty sterilize vial from storage.

Using aseptic technique, the pharmacist will gently swirl the contents of the vial containing aluminum hydroxide, withdraw 0.12 mL of the aluminum hydroxide and inject it into the empty sterilize vial (mixing vial). The pharmacist will then add 0.71 mL of Sterile Water for Injection to the mixing vial which contains 0.12 mL of aluminum hydroxide. The mixing vial should be gently swirled and inverted (do not shake). Next, the pharmacist will then gently swirl the vial containing gp145 C.6980 after which, using aseptic technique, the pharmacist will withdraw 0.17 mL (100 mcg) of gp145 C.6980 from the correct vial and inject it into the mixing vial (which contains aluminum hydroxide mixed with Sterile Water for Injection). After gentle swirling and inversion (do not shake vigorously) the pharmacist, using aseptic technique, will withdraw 1 mL of the mixed preparation for dosing into a 2, 3, or 5 mL size syringe. The pharmacist will apply an overlay to the syringe.

The syringe should be labeled as "HVTN 122 study product". The syringe must also be labeled for administration in the deltoid and "Gently roll the syringe prior to administration". This study product should be administered as soon as possible after preparation.

8.3.3 Placebo for gp145 C.6980 (Sodium Chloride for Injection, 0.9%) (Group 3)

Using aseptic technique, the pharmacist will withdraw 1 mL of Sodium Chloride for Injection, 0.9% into a 2, 3, or 5 mL size syringe. The pharmacist will apply an overlay to the syringe.

The syringe should be labeled as "HVTN 122 study product". The syringe must also be labeled for administration in the deltoid and "Gently roll the syringe prior to administration". In order to maintain the blind, the study product should be administered as soon as possible after preparation.

Any unused portion of vials or expired prefilled syringes is disposed of in accordance with institutional or pharmacy policy.

8.4 Administration

All injections are to be given IM in the deltoid.

When preparing a dose in a syringe and administering the dose, consideration should be given to the volume of solution in the needle before and after the dose is administered. Particularly, if the needle used to withdraw the product is replaced prior to vaccine administration, consideration should be given to conserving the full dose of product. The pharmacy and clinic staff members are encouraged to work together to administer the dose specified in the protocol.

The person administering the injection should gently roll the syringe prior to administration of the study product. These syringes will be labeled as "HVTN 122 study product".

Any administrator of study product will be blinded to the individual participant's treatment assignment. At sites where registered pharmacists are legally authorized to administer injections, the HVTN CRS may choose to have a blinded pharmacist administer vaccinations.

8.5 Acquisition of study products

gp145 C.6980 will be provided by the Division of AIDS, NIAID, NIH.

Aluminum Hydroxide Suspension will be provided by the Vaccine Research Center, NIAID, NIH.

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

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

8.6 Pharmacy records

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

8.7 Final disposition of study products

All unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by the CRPMC. The

procedures and relevant form are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

9 Clinical procedures

The schedule of clinical procedures is shown in Appendix F .

9.1 Informed consent

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

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

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

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

9.1.1 Screening consent form

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

Some HVTN CRSs have approval from their IRB/EC and any applicable RE to use a general screening consent form that allows screening for an unspecified HIV vaccine trial. In this way, HVTN CRS staff can continually screen potential participants and, when needed, proceed quickly to obtain protocol-specific

enrollment consent. Sites conducting general screening or prescreening approved by their IRB/EC and any applicable RE may use the results from this screening to determine eligibility for this protocol, provided the tests are conducted within the time periods specified in the eligibility criteria.

9.1.2 Protocol-specific consent forms

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

Each HVTN CRS is responsible for developing a protocol-specific consent form(s) for local use, based on the sample protocol-specific consent forms in Appendix A and Appendix C. 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 the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their 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 form includes instructions throughout the document for developing specific content.

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

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

9.1.3 Assessment of Understanding

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

An Assessment of Understanding is used to document the participant's understanding of key concepts in this HIV vaccine 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 vaccination 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;
- Complete physical examination, including height, weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Assessment of concomitant medications the volunteer is taking, including prescription and nonprescription drugs, vitamins, topical products, alternative/complementary medicines (eg, herbal and health food supplements), recreational drugs, vaccinations, and allergy shots;
- Laboratory tests as defined in the inclusion and exclusion criteria, including:
  - Screening HIV test
  - CBC with differential and platelet count
  - Chemistry panel (ALT, AST, ALP, and creatinine)
  - Urine dipstick (urinalysis if indicated, see Section 9.7)
  - HBsAg
  - Anti-HCV Ab

  - Syphilis test
  - Urine or serum pregnancy test (volunteers who were born female. 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.

- 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; and

- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in study inclusion criteria. Discussion of pregnancy prevention includes advising a participant who was born female and who reports no current sexual activity that could lead to that participant becoming pregnant to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

9.2.1 Use of screening results from another HVTN study

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

9.3 Enrollment and vaccination visits

Enrollment is simultaneous with first vaccination. The HVTN 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 vaccination visits, the following procedures are performed before vaccination:

- Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;

- Assessment of baseline reactogenicity parameters;

- Assessment of concomitant medications (as described in Section 9.2);

- Assessment of any new or unresolved AEs/intercurrent illnesses; and

- Urine or serum pregnancy test (for participants who were born female). Persons who are NOT of reproductive potential due to having undergone total 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 vaccination may proceed, vaccination is prepared and administered (see Sections 8.3 and 8.4).

Immediately following vaccination, the participant remains in the clinic for observation. An initial reactogenicity assessment is made at a target of 30 minutes after injection, with an acceptable range of 25-60 minutes. Before leaving the clinic, the participant is given the postvaccination memory tool and is instructed on how to complete it. The site will make arrangements to be in contact with the participant during the reactogenicity period (as described in Section 9.8).

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

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

- Pregnancy prevention assessment (as described in Section 9.2 and 9.6); 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).

Additional procedures will be performed at scheduled visits as specified in Appendix F:

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

- Assess for clinical evidence of vaccinia scarification; and

- Specimen collection (should be completed prior to vaccination).

9.4 Follow-up visits

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

- Risk reduction counseling (as described in Section 9.5);
- Pregnancy prevention assessment (as described in Section 9.2 and 9.6); and
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Assessment of new or continuing concomitant medications (as described in Section 9.2); and
- Assessment of new or unresolved AEs/intercurrent illnesses.

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

- Administration of the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
- Administration of a questionnaire that asks the participant about any HIV testing he or she may have received outside of the study. Participants will also be asked whether they believe they received the active vaccine or the control;
- HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- Abbreviated physical examination including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
- Specimen collection;
- 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 born female). 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.

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 current HVTN HIV testing algorithm following enrollment.

Participants will be counseled routinely during the trial on the avoidance of HIV infection and on the potential negative social impacts of testing antibody positive due to the vaccine. They will also be counseled on the risks of HIV antibody testing outside of the HVTN CRSs and will be discouraged from doing so during study participation and/or during any period of vaccine-induced positive serology.

Study staff will take particular care to 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. Such testing has become more likely due to the CDC's revised guidelines for HIV counseling and testing, as well as policy changes in many countries to make HIV testing more frequent and routine. CRS staff should 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 policies and regulations permit medical providers to perform HIV testing without first informing patients. If this is the case, then CRS staff should advise study participants that they may decline testing preemptively. CRS staff should also inform participants if positive results must be reported to local public health authorities. CRS staff should also inform participants of the need to maintain study blinding by getting HIV testing only at the study CRS. CRS staff should provide participants with CRS contact information and should encourage participants to ask medical providers to contact the CRS. The CRS can verify that the participant is in an HIV vaccine clinical trial and should only be tested at the study CRS.

Potential participants identified as being HIV infected during screening are not enrolled. All participants who become HIV infected during the study will be terminated from this study. Potential and enrolled participants identified as HIV infected will be referred for medical treatment, counseling, and management of the HIV infection. These individuals may also be referred to appropriate ongoing clinical trials or observational studies.

9.5.1 Distinguishing intercurrent HIV infection from vaccine-induced positive serology

The study product may elicit an antibody response to HIV proteins. Therefore, vaccine-induced positive serology may occur in this study. Several precautionary measures will be taken to distinguish intercurrent HIV infection from vaccine-induced positive serology. These precautionary measures include:

- Participants will have physical examinations at visits specified in Appendix F. Signs or symptoms of an acute HIV infection syndrome, an intercurrent illness consistent with HIV-1 infection, or probable HIV exposure would prompt a diagnostic workup per the HVTN algorithm for Recent Exposure/Acute Infection Testing to determine HIV infection.

- HIV testing will be performed at multiple timepoints throughout the study (see Appendix F). The Laboratory Program (or approved diagnostic laboratory) will follow the HVTN HIV testing algorithm (see Study Specific Procedures [SSP]), which is able to distinguish vaccine-induced antibody responses from actual HIV infections.

- All participants can receive HIV-1 diagnostic testing from the site following their last scheduled visit until they are told that they did not receive an HIV vaccine or that they do not have vaccine-induced seropositivity.

- All participants who received vaccine product and who have vaccine-induced positive or indeterminate HIV-1 serology (as measured by the standard anti-HIV antibody screening tests) at or after the study is unblinded will be offered poststudy HIV-1 diagnostic testing (per the HVTN poststudy HIV-1 testing algorithm) periodically and free of charge as medically/socially indicated (approximately every 6 months) unless or until HIV Ab testing is no longer the standard test in clinical settings.

9.5.2 VISP registry

Experimental HIV vaccines may induce antibody production to HIV antigens, producing reactive results on commercially available HIV test kits. This is called "vaccine-induced seropositivity" (VISP) (see Section 9.5.1). In order to provide poststudy HIV testing to distinguish between VISP and HIV infection, and to mitigate potential social harms resulting from VISP in HIV vaccine recipients who are not infected with HIV, the HVTN has created a VISP registry. Following study unblinding, the registry will allow trained staff to verify that an individual has received an HIV vaccine, and therefore has the potential for VISP. Information in the VISP registry will not be used for research. Rather, the registry exists to support provision of poststudy testing and counseling services to HIV vaccine recipients. The registry contains the names of all study participants, unless they request that their names be removed.

9.6 Contraception status

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

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

9.7 Urinalysis

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

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

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

9.8 Assessments of reactogenicity

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

The reactogenicity assessment period is 7 full days following each vaccination per the assessment schedule shown in Table 9-1. Participants are instructed to record symptoms using a postvaccination memory tool. Contact between the participant and the CRS staff should take place at least once within the 3 days following

vaccination. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 7 to resolution. Participants are instructed to contact the clinic for events that arise during the period between vaccination and the next scheduled visit. In general, a participant who self-reports any postvaccination reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity events are reported using CRFs that correspond to the time of assessment in Table 9-1. Reactogenicity assessments include assessments of systemic and local symptoms, vaccine-related lesions, and lymph nodes. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of vaccination and 7 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse event log form.

Table 9-1 Schedule of reactogenicity assessments

Day	Time	Performed by
0[a]	Baseline: before vaccination	HVTN CRS staff
	Early: 25-60 minutes after vaccination	HVTN CRS staff
	Between early assessment and 11:59pm day 0	HVTN CRS staff or participant
1-7[b]	Between 12:00am and 11:59pm on each of days 1-7	HVTN CRS staff or participant

[a] Day of vaccination

[b] New or unresolved reactogenicity symptoms present on day 7 are followed until resolution

9.8.1 Assessment of systemic and local symptoms

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

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

9.8.2 Assessment of injection site

Typical injection site reactions are erythema/redness and induration/swelling. The maximum horizontal and maximum vertical measurements for all injection site reactions are recorded.

All injection site reactions are monitored until resolution. Areas greater than 25 cm^2 are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

9.8.3 Assessment of lymph nodes

This assessment is required only when reactogenicity assessments are performed by HVTN CRS staff, not by the participant.

Only the proximally draining lymph nodes are assessed (eg, axillary nodes on the same side of the body for injections given in the deltoid). Lymph nodes are first evaluated for enlargement and tenderness. If they are found to be enlarged, measurements are taken to determine the size (widest diameter) of the enlarged node(s).

9.9 Visit windows and missed visits

Visit windows are defined in HVTN 122 Study Specific Procedures. For a visit not performed within the window period, a Missed Visit form is completed. If the missed visit is one that required safety assessments or local safety labs, HVTN CRS staff should attempt to bring the participant in for an interim visit as soon as possible.

Procedures performed at an interim visit are usually toxicity/safety assessments (including local safety labs) and HIV testing. With the exception of HIV testing, these procedures are performed only if they were required at the missed visit or if clinically indicated. HIV testing may be performed as deemed appropriate by the study staff. Blood samples for immunogenicity assays are not typically collected at interim visits.

If a missed visit required vaccination, please refer to Section 7.3.2 and Section 7.3.3 for resolution.

9.10 Early termination visit

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

9.11 Pregnancy

If a participant becomes pregnant during the course of the study, no more injections of study product will be given, but remaining visits and study procedures should be completed unless medically contraindicated or applicable regulations require termination from the study. If the participant terminates from the study prior to the pregnancy outcome, the site should make every effort to keep in touch with the participant in order to ascertain the pregnancy outcome. Pregnancies and pregnancy outcomes will be reported.

10 Laboratory

10.1 HVTN CRS laboratory procedures

The HVTN 122 Site Lab Instructions and SSP provide further guidelines for operational issues concerning the clinical and processing laboratories. This document includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

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

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

10.2 Total blood volume

Required blood volumes per visit are shown in Appendix E. 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 Primary immunogenicity timepoints

The primary immunogenicity timepoints in this study occur 2 weeks after the first and third vaccinations. Endpoint assays for humoral and cellular responses are performed on participants at the primary immunogenicity timepoints and may be performed at baseline. Depending on the number of responders observed, assays for humoral and cellular responses may be performed on participants at other timepoints; the schedule is shown in Appendix E.

10.4 Endpoint assays: cellular

10.4.1 Flow cytometry

Flow cytometry will be used to examine vaccine-specific CD4+ and CD8+ T-cell responses following stimulation of PBMCs with synthetic HIV peptides that span the proteins encoded by the vaccine. ICS parameters will include cytokines such as IFN-γ, interleukin (IL)-2, and tumor necrosis factor (TNF)-α, and may include other cytokines (such as cytokines relevant to Th2 and Th17 responses) to identify T cells of specific functionality. Markers of cytotoxic potential (eg, Granzyme B)

and of Tfh functionality (eg, CXCR5 and PD-1) may also be included. Data will be reported as percentages of CD4+ or CD8+ T cells responding to a specific peptide pool. Additional cell surface markers, cytokines, or functional markers may also be analyzed.

10.5 Endpoint assays: humoral

10.5.1 Binding antibody multiplex assay

HIV-specific IgG antibodies will be assessed on plasma/serum samples from study participants taken at the primary immunogenicity timepoints and baseline. IgG subclass and IgA assays may also be performed. Specimens from other timepoints may also be assayed based on the results of the initial assay.

10.5.2 Neutralizing antibody assay

HIV-1–specific nAb assays will be performed on serum samples from study participants taken at the primary immunogenicity timepoints. Specimens from the baseline and other timepoints may also be analyzed at the discretion of the HVTN Laboratory Program, which may be contingent on the results of the primary immunogenicity timepoints. The TZM-bl assay will test neutralization of the vaccine strain (CO6980) and a single highly neutralization-sensitive Tier 1 virus as a positive control (MW965.26). The global panel and/or clade-specific panels may be used to assess Tier 2 neutralization [41,42].

10.6 Genotyping

Molecular human leukocyte antigen (HLA) typing may be performed on enrolled participants using cryopreserved PBMC collected at baseline, initially on specimens from participants who demonstrate vaccine-induced T-cell responses at postvaccination timepoints. Other participants (including control recipients) may be HLA-typed to support future studies of immunological interest at the discretion of the HVTN Laboratory Program. Other markers, such as genes associated with immune responses or HIV-1disease progression may also be assessed.

10.7 Lab assay algorithm

The Lab Assay Algorithm lists assays to characterize cellular, humoral, and innate immune responses as well as host genetics that may be conducted to determine endpoints in HVTN vaccine trials. The type of assay(s) employed will be dependent on the response obtained by the primary immunogenicity assays at relevant timepoints. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

10.8 Exploratory studies

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

10.8.1 Tfh phenotyping

Flow cytometry may be used to identify peripheral blood follicular helper T (pTfh) cells and peripheral T follicular regulatory (pTfr) cells. Phenotyping of pTfh and pTfr cells will be based on expression of CXCR5, PD-1, CD127, and CD25 on CD4+ T cells, and may include additional markers. For example, if flow cytometry panels are successfully developed to assess CD69, OX40, IL-21, and CD154 expression as a functional read-out, vaccine-specific Tfh cells may be assessed and isolated for further analysis.

10.8.2 B cell plasmablasts

Flow cytometry may be used to identify the early precursors for antibody-secreting B cells, called B cell plasmablasts, in the peripheral blood. Plasmablasts will be mainly characterized by CD19+ CD20- and high expression of CD27 and CD38. The flow cytometry panels might also include additional markers and assessment of antigen specificity.

10.8.3 Vaccinia neutralizing antibody assay

Neutralizing antibody assays may be performed on serum samples collected at baseline to assess participant exposure to vaccinia.

10.9 Specimen storage and other use of specimens

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

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

This research may relate to HIV, vaccines, the immune system, and other diseases. This could include limited genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each CRS's informed consent form, or as otherwise authorized under applicable law. Other testing on specimens ("other use") will occur only after review and approval by the HVTN, the IRB/EC of the researcher requesting the specimens, and the CRS's IRBs/ECs/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 HVTN 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 122 PSRT

The HVTN 122 PSRT is composed of the following members:

- DAIDS medical officer representative,
- Protocol chair and cochair,
- Protocol Team leader,
- Core medical monitor, and
- Clinical safety specialist.

The clinician members of HVTN 122 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, clinical data manager, vaccine developer representative, clinical trial manager, and others may also be included in HVTN 122 PSRT meetings.

11.1.2 HVTN SMB

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

The SMB reviews safety data, unblinded as to treatment arm, approximately every 4 months. The reviews consist of evaluation of cumulative reactogenicity events, AE, laboratory safety data, and individual reports of adverse events requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 122 PSRT.

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

11.1.3 SDMC roles and responsibilities in safety monitoring

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

- Maintaining a central database management system for HVTN clinical data; and

- Providing reports of clinical data to appropriate groups such as the HVTN 122 PSRT and HVTN SMB (see Section 11.1.2).

11.1.4 HVTN Core roles and responsibilities in safety monitoring

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 122 PSRT AE review criteria (see Section 11.4);

- Notifying HVTN CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.4);

- Querying HVTN CRSs for additional information regarding reported clinical data; and

- Providing support to the HVTN 122 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

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

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). All AEs are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, dated July 2017, available on the RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables, except:

- Unintentional weight loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 122 Study Specific Procedures);

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

During the study period, all AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (Section 11.2.3) and (2) if the AE meets the criteria for a safety pause/prompt AE review (Section 11.4).

Sites are expected to notify HVTN clinical safety staff of any serious safety concern requiring their attention (see 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/hvtn122). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

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

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

11.2.3 Expedited reporting of adverse events to DAIDS

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

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

The study products for which expedited reporting are required are:

- gp145 C.6980 with aluminum hydroxide adjuvant

- placebo (Sodium Chloride for Injection, 0.9%)

The expedited reporting period for this study comprises the entire study period for each individual participant (from study enrolment until study completion or discontinuation from the study). During this period the SAE Reporting Category will be used.

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

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). 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.

If the PSRT believes unblinding is appropriate (eg, if unblinding to treatment assignment will assist with the clinical management of the SAE), the PSRT will consult the independent HVTN SMB for a recommendation. In the event the HVTN SMB determines that unblinding is indicated, the SMB will inform the individual (eg, site physician) of the participant's treatment assignment in such a manner as to maintain the study blind of the PSRT and study team. For additional impact and management of SAEs on the study, see Section 11.4.

11.3 Initial safety evaluation

Enrollment will proceed in all groups simultaneously and will be restricted to a maximum of 1 participant per day until 5 participants in Group 1, 3 participants in Group 2 and 1 placebo recipient in Group 3 have been enrolled. The HVTN 122 PSRT will review the cumulative safety data through 2 weeks postvaccination on each of these participants and will determine whether it is safe to proceed with full enrollment.

11.4 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and vaccination 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 122 PSRT AE review are summarized in Table 11-1. Vaccinations 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 122 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of vaccinations are listed in Section 7.3.

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

Event and relationship to study products	Severity	HVTN CRS action[a]	HVTN Core action
SAE, related	Grade 5 or Grade 4	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate HVTN 122 PSRT notification
SAE, related	Grade 3	Email and submit forms immediately	Immediate HVTN 122 PSRT notification and prompt HVTN 122 PSRT AE review to consider pause
AE[b], related	Grade 3 or Grade 4	Email and submit forms immediately	Immediate HVTN 122 PSRT notification and prompt HVTN 122 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/hvtn###).

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

For all safety pauses, HVTN Core notifies the HVTN 122 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the SMB.

Once a trial is paused, the HVTN 122 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of vaccination is appropriate, consulting the SMB if necessary. HVTN Core notifies the participating HVTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study vaccinations. Based on the HVTN 122 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 122 PSRT notification or prompt HVTN 122 PSRT AE review is triggered, HVTN Core notifies the HVTN 122 PSRT as soon as possible during working hours (US Pacific Time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 122 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

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

In addition, all other AEs are reviewed routinely by the HVTN 122 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 HVTN CRSs. Events are tracked by internal reports until resolution.

11.5.1 Daily review

Blinded daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 122 PSRT AE review criteria.

11.5.2 Weekly review

During the injection phase of the trial, the HVTN 122 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. After the injections and the final 2-week safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 122 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the HVTN CRS clinic coordinator for verification.

11.6 Study termination

This study may be terminated early by the determination of the HVTN 122 PSRT, the US FDA, NIH, Office for Human Research Protections (OHRP), or vaccine developer(s). In addition, the conduct of this study at an individual HVTN CRS may be terminated by the determination of the IRB/EC and any applicable RE.

12 Protocol conduct

This protocol and all actions and activities connected with it will be conducted in compliance with the principles of GCP (ICHe6), and according to DAIDS and HVTN policies and procedures as specified in the *HVTN Manual of Operations,* DAIDS Clinical Research Policies and Standard Procedures Documents including procedures for the following:

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

Any policies or procedures that vary from DAIDS and HVTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 122 *Study Specific Procedures.*

12.1 Social impacts

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

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

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

12.2 Emergency communication with study participants

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

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

13 Version history

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

The version history of, and modifications to, Protocol HVTN 122 are described below.

Protocol history and modifications

Date: September 27, 2017

Protocol version: Version 1.0
Protocol modification: Original protocol

14 Document references (other than literature citations)

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

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
- Division of AIDS Protocol Registration Manual. Available at https://www.niaid.nih.gov/sites/default/files/prmanual.pdf
- Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, dated July 2017. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 122 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 122 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN 122 Site Lab Instructions. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.
- Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at http://www.iata.org/ps/publications/dgr/Pages/index.aspx

- Lab assay algorithm (available upon request)

- International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

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

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

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

- Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials. Available at https://www.niaid.nih.gov/sites/default/files/daids-sourcedocpolicy.pdf

- Title 21, Code of Federal Regulations, Part 50. Available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50

- Title 45, Code of Federal Regulations, Part 46. Available at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html

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

15 Acronyms and abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AVEG	AIDS Vaccine Evaluation Group
BAMA	binding antibody multiplex assay
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
COMPASS	Combinatorial Polyfunctionality analysis of Antigen-Specific T-cell Subsets
CRF	case report form
CRPMC	NIAID Clinical Research Products Management Center
CRS	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS (US NIH)
DHHS	US Department of Health and Human Services
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FS	functionality score
GCP	Good Clinical Practice
HBsAG	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HVTN	HIV Vaccine Trials Network
IB	Investigator’s Brochure
ICH	International Conference on Harmonisation

ICS	intracellular cytokine staining
IFN-γ	interferon gamma
IgA	immunoglobulin A
IgG	immunoglobulin G
IL-2	interleukin 2
IM	intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
MedDRA	Medical Dictionary for Regulatory Activities
MHRP	(US) Military HIV Research Program
MIMOSA	Mixture Models for Single-cell Assays
MMR	measles, mumps, and rubella
MPER	membrane-proximal external region
MVA	modified vaccinia Ankara
nAb	neutralizing antibody
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NIH	US National Institutes of Health
OHRP	US Office for Human Research Protections
OPV	oral polio vaccine
PAB	DAIDS Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PCA	principal component analysis
PCR	polymerase chain reaction
PFS	polyfunctionality score
PI	Principal Investigator
PSRT	Protocol Safety Review Team
pTfh	peripheral T follicular helper (cells)
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SMB	Safety Monitoring Board
SPT	DAIDS Safety and Pharmacovigilance Team
TB	tuberculosis
Tfh	T follicular helper (cells)
Tfr	T follicular regulatory (cells)
TNF-α	tumor necrosis factor - alpha

UW-VSL	University of Washington Virology Specialty Laboratory
VISP	Vaccine induced seropositivity
VRC	Vaccine Research Center (NIAID)
WBC	white blood cell

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Appendix A Sample informed consent form

Title: A phase 1 double-blind, randomized clinical trial to evaluate the safety and immunogenicity of a recombinant oligomeric gp145 clade C Env protein (gp145 C.6980) in healthy, HIV-1–uninfected adult participants in the US

HVTN protocol number: HVTN 122

Site: [Insert site name]

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

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

About the study

The HIV Vaccine Trials Network (HVTN) and [Insert site name] are doing a study to test an HIV vaccine. HIV is the virus that causes AIDS.

About 45 people will take part in this study at multiple sites. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

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

   - Is the study vaccine safe to give to people?
   - Are people able to take the study vaccine without becoming too uncomfortable?
   - How do people's immune systems respond to the study vaccine? (Your immune system protects you from disease.)

2. **The study vaccine cannot give you HIV.**

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

3. **We do not know if the study vaccine will decrease, increase, or not change your risk of becoming infected with HIV if you are exposed to the virus.**

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

Several studies have tested whether HIV vaccines can reduce the risk of getting HIV from another person. In some studies, people who got the vaccine seemed to have the *same* risk of getting HIV as people who did not get the vaccine. In one study, people who got the vaccine seemed to have a *lower* risk of getting HIV than people who did not get the vaccine. In studies with a different vaccine, some people who got the vaccine had a *higher* risk of getting HIV than people who did not get the vaccine.

We do not know whether the vaccine in this study will affect your risk of getting HIV from another person. The risk could be higher, lower, or unchanged. It's very important to avoid exposure to HIV during and after the study. We will tell you how to avoid HIV.

4. This study vaccine is experimental.

The study vaccine is called gp145 C.6980. From here on, we will call it gp145 or the study vaccine. It is an experimental HIV vaccine. That means we do not know if the vaccine will be safe to use in people, or if it will work to prevent HIV infection. This vaccine is used only in research studies.

The vaccine was developed by the US Military HIV Research Program and is being supplied for this study by the Division of AIDS at the US National Institutes of Health.

This protein vaccine is a man-made copy of a piece of a protein found on the outside of HIV. This protein has been changed in order to strengthen the immune response made by the body's immune system. This protein is mixed with an adjuvant called alum. An adjuvant is something added to the vaccine to help the immune system respond better. Alum is the most widely used vaccine adjuvant. It has been used in licensed vaccines given to hundreds of millions of people all over the world.

This study vaccine has not been given to people before. In one study it was tested in monkeys in combination with another vaccine without causing health problems (no changes in weight or temperature). Similar HIV protein vaccines mixed with alum adjuvant have been given to more than 12,000 people in clinical trials without causing any serious health problems.

General risks of vaccines:

All vaccines can cause fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired. Vaccines can also cause pain, redness, swelling, or itching where you got the injection. Most people can still do their planned activities after getting a vaccine. Rarely, people have side effects that limit their normal activities or make them go to the doctor.

Rarely, a vaccine can cause an allergic reaction, including a rash, hives, or trouble breathing. Allergic reactions can be life-threatening. You should tell us if you have ever had a bad reaction to any injection or vaccine.

Very rarely, a vaccine causes an autoimmune disease in a person, or makes an autoimmune disease worse. An autoimmune disease happens when your immune system attacks your own body, instead of attacking an infection.

Joining the study

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

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

   If you join this study, you may not be allowed to join other HIV vaccine or HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. 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 6 if you use a separate screening consent that covers these procedures.

6. **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)

   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 Hepatitis B, Hepatitis C, and syphilis. We will ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV. If you were born female, we will test you for pregnancy.

   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)

7. **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.

8. **If you were born female and could become pregnant, you must agree to use birth control to join this study.**

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

You should not become pregnant during the study because we do not know how the study vaccine could affect the developing baby. You must agree to use effective birth control from 21 days before your first injection until 6 months after your last study injection. 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:

9. **You will come to the clinic for scheduled visits about [#] times over [Insert period of time].**

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

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

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

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

10. **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).

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.

11. We will give you either the study vaccine or a placebo.

Not everyone in this study will get the study vaccine. Some people will get a placebo, a substance that does not contain vaccine. We will compare the results from people who got the placebo with results from people who got the study vaccine. In this study, the placebo is sterile salt water.

You have a 8-in-9 chance of getting the study vaccine. *Site: Modify the randomization metaphor in the next sentence as appropriate to your local culture.* Whether you get the study vaccine or the placebo is completely random, like flipping a coin.

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

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

12. We will give you the study vaccine on a schedule.

You will be in one of 3 groups. You will get injections of the study vaccine or placebo into the upper arm. This will happen 3 times during the study.

		Injection Schedule		
	Number	First injection	2 months later	6 months later
Group 1	25	High dose gp145 + alum	High dose gp145 + alum	High dose gp145 + alum
Group 2	15	Low dose gp145 + alum	Low dose gp145 + alum	Low dose gp145 + alum
Group 3	5	placebo	placebo	placebo

You will have to wait in the clinic for about a half hour after each injection to see if there are any problems. Then that night and for 7 more days, you will need to keep track of how you are feeling and if you have any symptoms. Within 3 days of your injections, we will also ask you how you are doing. You should always contact us if you have any issues or concerns after getting an injection. If you have a problem, we will continue to check on you until it goes away.

13. In addition to giving you the study vaccine, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV;
- Do physical exams;
- Do pregnancy tests if you were born female;
- Ask questions about your health, including medications you may be taking;
- Ask questions about any personal problems or benefits you may have from being in the study;
- Test your body's response to some vaccines you may have gotten previously; and
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 17 mL and 180 mL (a little more than 1 tablespoon to ¾ cup). Your body will make new blood to replace the blood we take out.

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

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

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

14. We will counsel you on avoiding HIV infection.

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

15. The HVTN will test your samples to see how your immune system responds to the study products.

We will send your samples (without your name) to labs approved by the HVTN for this study. In rare cases, some of your samples may be sent to labs approved by the HVTN in other countries for research related to this study.

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

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

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

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

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

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

16. When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies and share them with other researchers.

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

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

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

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

Will I be paid for the use of my samples? No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens,

there is no plan to share any money with you. The researcher is not likely to ever know who you are.

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

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

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

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

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

Researchers may also do genetic testing on your samples.

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

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

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

People who may see your information are:

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

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

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

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.

Site: Any change to the following boxed text requires approval from HVTN Regulatory Affairs.

We do need to share your name with the HVTN in case you need proof in the future that you participated in an HIV vaccine study. The HVTN will keep your name in a secure file with these items:

- The name of your study
- Your age or date of birth
- Your study ID number
- What study product(s) you received

There are no HIV test results kept in this file. The HVTN will not share any information that could identify you without your agreement. The HVTN will remove your name from the file if you do not want it there.

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,
- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- [Insert name of product developer] and people who work for them,
- The HVTN and people who work for them,
- The HVTN Safety Monitoring Board, and
- The US Office for Human Research Protections.

All reviewers will take steps to keep your records private.

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

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

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

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.

18. We may stop your injections 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 injections.

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 injections, we may ask you to stay in the study to complete other study procedures.

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

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

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

20. If you get infected with HIV during the study, we will help you get care and support.

You will not be able to stay in this study. We will counsel you about your HIV infection and about telling your partner(s). We will tell you where you can get support and medical care. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

Other Risks

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

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

Risks of routine medical procedures:

In this study, we will do some routine medical procedures. These are taking blood and giving injections. These procedures can cause bruising, pain, fainting, soreness, redness, swelling, itching, a sore, bleeding, and (rarely) muscle damage

or infection where you got the injection. Taking blood can cause a low blood cell count (anemia), making you feel tired.

Personal problems/discrimination/testing HIV antibody positive:

About 10 to 20% of people who join HVTN studies report personal problems or discrimination because of joining an HIV vaccine 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.

The body makes antibodies to fight or prevent infection. Most vaccines cause the body to make antibodies as a way of preventing infection. Your body may make antibodies to HIV because you received an HIV study vaccine. The study vaccine may cause you to test positive on some types of HIV antibody tests, even if you are not infected with HIV. This is called vaccine-induced seropositivity (VISP). VISP means that after you get the study vaccine, a routine HIV test done outside this clinic may say you have HIV, even if you don't. For this reason, you should plan to get HIV tests only at this clinic during the study. Our tests can tell the difference between true HIV infection and a positive result that is caused by the study vaccine.

If you have a positive test result caused by the study vaccine at any time, we can arrange free HIV testing for as long as you need it. If this happens, we do not know how long you will test positive due to the study vaccine. If you receive a positive HIV test result and we determine it is because you have HIV, we will refer you for follow-up care.

It is unlikely, but you could test negative at the end of the study and positive some time later, even though you don't have HIV. This could happen if different HIV tests come into use. We will give you a phone number to call for more information.

Site: Modify the following paragraph if applicable. If someone believes you are infected with HIV even if you are not, you could face discrimination and other problems. For example, in some countries, you could be denied medical or dental care, employment, insurance, a visa, or entry into the military. If you do have a positive HIV antibody test caused by the study vaccine, you will not be able to donate blood or organs. Your family and friends may treat you differently. We will give you a brochure that tells you more about testing HIV positive because of an HIV vaccine, and how you can avoid some of these problems.

If you become pregnant during or after the study and have VISP, we don't know if the antibodies could be passed to your baby. We know that this happens with other vaccines, like tetanus vaccine. These antibodies from the mother are not a danger to the baby, and they go away over time. For most babies antibodies from the mother last for about 6 months.

You should always tell the delivery staff if you have VISP. However, you may still be tested for HIV using the antibody test when you deliver your baby. If your test is positive and the delivery staff believes you have an HIV infection, your baby may be started on antiretroviral treatment when it is not needed. If this happens, we can arrange for you and the baby to have a test that can tell the difference between true HIV infection and a VISP result. If you or the baby continue to have VISP, we can arrange this testing for free for as long as it is needed.

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

We do not know if getting this study vaccine will affect how you respond to any future approved HIV vaccine. It could be that a future HIV vaccine may not work

as well for you because you got the study vaccine. Currently, no HIV vaccine has been approved for use.

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

Benefits

22. The study may not benefit you.

We do not know whether getting the study vaccine might benefit you in any way. However, being in the study might still help you in some ways. The counseling that you get as part of the study may help you avoid getting HIV. The lab tests and physical exams that you get while in this study might detect health problems you don't yet know about.

This study may help in the search for a vaccine to prevent HIV. However, if the study vaccine later become approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

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

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

Leaving the study

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

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

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

Injuries

Site: Approval from HVTN Regulatory Affairs (at vtn.core.reg@hvtn.org) is needed for any change (other than those that the instructions specifically request or those previously approved by HVTN Regulatory Affairs) to the boxed text.

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

Your health is important to us. *(Site: 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 vaccine or the adjuvant and/or procedures. If it is, we call it a study-related injury. There are funds to pay for treatment of study-related injuries if certain conditions are met.

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

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

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

Questions

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

If you have questions about this study, contact
[name 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 or other appropriate organization] 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 the following section if using a separate consent for use of samples and information in other studies

27. In Section 16 of this form, we told you about possible other uses of your extra samples and information, outside this study. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN keeps track of your decision about how your samples and information can be used.

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

OR

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

OR

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

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

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

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

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

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

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

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

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

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

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

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

You must agree to use effective birth control from 21 days before your first injection until 6 months after your last study injection.

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 female partner or partners;
- You only have oral sex; or,
- You are sexually abstinent (no sex at all).

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

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

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

Title: A phase 1 double-blind, randomized clinical trial to evaluate the safety and immunogenicity of a recombinant oligomeric gp145 clade C Env protein (gp145 C.6980) in healthy, HIV-1–uninfected adult participants in the US

HVTN protocol number: HVTN 122

Site: [Insert site name]

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

The HVTN calls these samples 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 sell my samples and information?**

   No, but the HVTN may share your samples with other researchers. Once we share your samples and information, we may not be able to get them back.

7. How do other researchers get my samples and information?

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

8. What information is shared with HVTN or other researchers?

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

9. What kind of studies might be done with my extra samples and information?

The studies will be related to HIV, vaccines, the immune system and other diseases.

Researchers may also do genetic testing on your samples.

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

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

10. What are the risks of genetic testing?

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

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

Questions

12. If you have questions or problems about allowing your samples and information to be used in other studies, use the following important contacts.

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact
[name 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 of person on IRB or other appropriate organization].

13. Please choose only one of the options below and write your initials or make your mark in the box next to it. Whatever you choose, the HVTN keeps track of your choice about how your samples and information can be used.

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

OR

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

OR

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

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

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

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

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

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

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

			Time after 1st injection visit								
Procedure	Screening visit(s)	First injection visit	1 week	2 weeks	2 months (2nd injection visit)	2½ months	6 months (3rd injection visit)	6 months + 1 week	6½ months	9 months	12 months
Injection		√			√		√				
Medical history	√										
Complete physical	√										√
Brief physical		√	√	√	√	√	√	√	√	√	
Urine test	√			√					√		
Blood drawn	√	√	√	√		√	√	√	√	√	√
Pregnancy test (participants born female)*	√	√			√		√			√	
HIV testing & pretest counseling	√					√	√			√	√
Risk reduction counseling	√	√		√	√	√	√		√	√	√
Questions/questionnaire	√	√	√	√	√	√	√	√	√	√	√

Not shown in this table is a time after all study participants have completed their last scheduled visit when you can find out what product you received.

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

Appendix E Laboratory procedures

					Tube volume (mL)											Total
				Visit:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	
				Day:	Screening visit[3]	D0	D7	D14	D56	D70	D168	D175	D182	D273	D364	
				Week:		W0	W1	W2	W8	W10	W24	W25	W26	W39	W52	
				Month:		M0	M0.25	M0.5	M2	M2.5	M6	M6.25	M6.5	M9	M12	
						VAC1			**VAC2**		**VAC3**					
Procedure	**Ship to[1]**	**Assay Location[2]**	**Tube[4]**	**Tube size (vol. capacity)[4]**												
BLOOD COLLECTION																
Screening or diagnostic assays																
Screening HIV test	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	5
HBsAg/anti-HCV	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	5
Syphilis	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	5
HIV diagnostics[9]	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	10	10	—	—	10	20[9]	50
Safety labs																
CBC/ Diff/ platelets	Local lab	Local lab	EDTA	5mL	5	—	—	5	—	5	—	—	5	5	—	25
Chemistry panel[5]	Local lab	Local lab	SST	5mL	5	—	—	5	—	5	—	—	5	5	—	25
Immunogenicity assays[6]																
Host genetics[7]	CSR	HVTN Labs	ACD	8.5mL	—	17	—	—	—	—	—	—	—	—	—	17
Cellular assays																
ICS	CSR	HVTN Labs	ACD	8.5mL	—	42.5	—	42.5	—	42.5	—	—	***42.5***	—	42.5	212.5
pTfh, pTfr, and plasmablasts	CSR	HVTN Labs	ACD	8.5mL	—	z	42.5	—	—	—	42.5	42.5	—	—	—	127.5
Humoral assays																
Binding Ab	CSR	HVTN Labs	SST	8.5mL	—	8.5	—	***8.5***	—	8.5	—	—	***8.5***	—	8.5	42.5
Neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	8.5	—	8.5	—	8.5	—	—	***8.5***	—	8.5	42.5
Vaccinia neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	—	—	—	—	—	0
Specimen storage																
PBMC	CSR		ACD	8.5mL	—	42.5	—	42.5	—	42.5	—	—	42.5	—	68	238
Serum	CSR		SST	8.5mL	—	17	—	17	—	17	—	—	17	—	17	85
Visit total					**25**	**136**	**42.5**	**129**	**0**	**139**	**52.5**	**42.5**	**129**	**20**	**164.5**	**880**
56-Day total					**25**	**161**	**203.5**	**332.5**	**332.5**	**268**	**52.5**	**95**	**224**	**20**	**164.5**	
URINE COLLECTION																
Urine dipstick[10]	Local lab	Local lab			X	—	—	X	—	—	—	—	X	—	—	
Pregnancy test[8]	Local lab	Local lab			X	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)

[3] Screening may occur over the course of several contacts/visits up to and including day 0 prior to vaccination.

[4] Local labs may assign appropriate alternative tube types for locally performed tests.

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment) and Section 9.3 (postenrollment).

[6] Immunogenicity assays will be performed at M0 and M0.5 (for binding Ab assay) and M6.5. Based on the number of responders observed at these timepoints, lab assays may be performed on participants for humoral and cellular responses at other timepoints

[7] Genotyping may be performed on enrolled participants using cryopreserved PBMC collected at baseline, initially in participants who demonstrate vaccine-induced T-cell responses at postvaccination timepoints.

[8] For a participant who was born female, pregnancy test must be performed on the day of vaccination with negative results received prior to vaccination. 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.

[9] At an early termination visit for a withdrawn or terminated participant (see Section 9.10), blood should be drawn for HIV diagnostic testing, as shown for visit 11 above.

[10] And microscopy if needed.

y = SST blood collected for serum storage will also cover specimen needs for the Vaccinia neutralizing Ab assay; no separate blood draw is needed.

z = ACD blood collected for PBMC storage will also cover specimen needs for the pTfh, pTfr, and plasmablasts assay; no separate blood draw is needed.

Appendix F Procedures at HVTN CRS

Visit:	**01**[1]	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**Post**
Day:		D0	D7	D14	D56	D70	D168	D175	D182	D273	D364	
Month:		M0	M0.25	M0.5	M2	M2.5	M6	M6.25	M6.5	M9	M12	
Procedure	Scr.	VAC1			VAC2		VAC3					
Study procedures[2]												
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	—	—	—	—	—	—	—	—	—	X	—
Abbreviated physical exam	—	X[3]	X	X	X	X	X	X	X	X	—	—
Risk reduction counseling	X	X	—	X	X	X	X	—	X	X	X	—
Pregnancy prevention assessment[4]	X	X	X	X	X	X	X	X	X	X	X	—
Behavioral risk assessment	X	—	—	—	—	X	X	—	—	X	X	—
Confirm eligibility, obtain demographics, randomize	X	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	X	X	X	X	X	X	X	X	X	—
Social impact assessment questionnaire	—	—	—	—	—	X	X	—	—	—	X	—
Outside testing and belief questionnaire	—	—	—	—	—	—	X	—	—	—	X	—
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	—
Intercurrent illness/adverse experience	—	X	X	X	X	X	X	X	X	X	X	—
HIV infection assessment[5]	X	—	—	—	—	X	X	—	—	X	X	—
Confirm HIV test results provided to participant	—	X	—	—	—	—	X	—	X	—	X	X
Local lab assessment												
Urine dipstick	X	—	—	X	—	—	—	—	X	—	—	—
Pregnancy (urine or serum HCG)[6]	X	X	—	—	X	—	X	—	—	X	—	—
CBC, differential	X	—	—	X	—	X	—	—	X	X	—	—
Chemistry panel (see Section 9.2)	X	—	—	X	—	X	—	—	X	X	—	—
Syphilis, Hepatitis B, Hepatitis C	X	—	—	—	—	—	—	—	—	—	—	—
Vaccination procedures												
Vaccination[7]	—	X	—	—	X	—	X	—	—	—	—	—
Reactogenicity assessments[8]	—	X	—	—	X	—	X	—	—	—	—	—
Poststudy												
Unblind participant	—	—	—	—	—	—	—	—	—	—	—	X

[1] Screening may occur over the course of several contacts/visits up to and including day 0 prior to vaccination.

[2] For specimen collection requirements, see Appendix E.

[3] Includes exam for clinical evidence of vaccinia scarification.

[4] Pregnancy prevention assessment is required only for participants who were born female and are capable of becoming pregnant.

[5] Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant.

[6] For a participant who was born female, pregnancy test must be performed on urine or blood specimens within 24 hours of vaccination with negative results received prior to vaccination. Pregnancy test to determine initial eligibility may be performed at screening, but must also be done on day 0 prior to first vaccination. 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. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test.

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

[8] Reactogenicity assessments performed daily for at least 7 days postvaccination (see Section 9.8).

Appendix G Protocol Signature Page

A phase 1 double-blind, randomized clinical trial to evaluate the safety and immunogenicity of a recombinant oligomeric gp145 clade C Env protein (gp145 C.6980) in healthy, HIV-1–uninfected adult participants in the US

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies

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

DAIDS Protocol Number: HVTN 122

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