HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 123

A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1–uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

DAIDS DOCUMENT ID 34569

IND 017488 HELD BY DAIDS

CLINICAL TRIAL SPONSORED BY

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

STUDY PRODUCTS PROVIDED BY

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

December 12, 2018
Final
HVTN 123, Version 1.0

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and/or 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. If a program for antiretroviral therapy (ART) provision is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.

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

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

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

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

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

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

2 IRB/EC review considerations

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

2.1 Minimized risks to participants

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

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants 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 and 5 and 21 CFR 56.111 (a) 4 and 5: Informed consent is sought from each prospective subject or the subject's legally authorized representative as required by 45 CFR 46.116 and 21 CFR Part 50; informed consent is appropriately documented as required by 45 CFR 46.117 and 21 CFR 50.27

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

2.5 Adequate safety monitoring

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

This protocol has extensive safety monitoring in place (see Section 11). Safety is monitored daily by HVTN Core and routinely by the HVTN 123 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 National Institutes of Health (NIH), which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs an Agreement on Confidentiality and Use of Data and Specimens with the HVTN. In some cases, a comparable confidentiality agreement process may be acceptable. Each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

3 Overview

Title

A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1–uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

Primary objective(s)

- To evaluate and compare the safety and tolerability of the CH505TF gp120 proteins produced by transient and stable transfection in HIV-1–uninfected, healthy adults

- To evaluate and compare the magnitude of binding antibody responses elicited by the CH505 TF gp120 proteins produced via transient and stable transfection methods

Study products and routes of administration

- **Stable**: CH505TF gp120 developed via upstream stable transfection of CHO-DG44 cell line, mixed with GLA-SE (glucopyranosyl lipid A in a stable emulsion [oil-in-water emulsion containing squalene])

- **Transient**: CH505TF gp120 developed via upstream transient transfection of CHO-S cell line, mixed with GLA-SE

Table 3-1 Schema

Study arm	n	Month 0	Month 2	Month 6
Group 1	15	100 mcg CH505TF gp120 **Stable**	100 mcg CH505TF gp120 **Stable**	100 mcg CH505TF gp120 **Stable**
Group 2	15	100 mcg CH505TF gp120 **Transient**	100 mcg CH505TF gp120 **Transient**	100 mcg CH505TF gp120 **Transient**
Total	30			

Notes

GLA-SE will be admixed with all proteins. The total dose of GLA-SE will be 10 mcg at all timepoints. The total volume for protein plus adjuvant for injection is 1 mL, mixed 1:1 by volume. All injections will be administered intramuscularly (IM) by needle and syringe.

Participants

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

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

12 months of scheduled clinic visits (main study) followed by an Adverse Events of Special Interest (AESI) health contact at month 18

Estimated total study duration

21 months (includes enrollment, follow-up, and AESI health contact)

Investigational New Drug (IND) sponsor

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

Study product providers

- Stable CH505TF gp120: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- Transient CH505TF gp120: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)
- GLA-SE adjuvant: DAIDS, NIAID, NIH, DHHS (Bethesda, Maryland, USA)

Core operations

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

Statistical and data management center (SDMC)

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

HIV diagnostic laboratory

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

Endpoint assay laboratories

- Duke University Medical Center (Durham, North Carolina, USA)

- Fred Hutch/University of Washington (Seattle, Washington, USA)

Study sites

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

Safety monitoring

HVTN 123 PSRT; HVTN SMB

3.1 Protocol Team

Protocol leadership

Chair	Greg Wilson Vanderbilt Medical Center 615-343-5731 greg.wilson@vumc.org	*Statistician*	Youyi Fong SCHARP, Fred Hutch 206-667-1093 yfong@fredhutch.org
Co-chair	Colleen Kelley Emory University 404-712-1435 colleen.kelley@emory.edu	*Medical officer*	Maggie Brewinski Isaacs DAIDS, NIAID 301-761-7009 maggie.brewinskiisaacs@nih.gov
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Other contributors to the original protocol

Core medical monitor	Carmen Paez HVTN Core, Fred Hutch	*Clinical safety specialist*	Maija Anderson HVTN Core, Fred Hutch
Study product developer representatives	Tony Moody Duke University	*Clinical trials manager*	Julie Hunt HVTN Core, Fred Hutch
	Zachary Sagawa IDRI	*Statistical research associate*	Yiwen Lu SCHARP, Fred Hutch
DAIDS protocol pharmacist	Katherine Shin DAIDS, NIAID 240-627-3047	*SDMC Associate director of lab science*	April Randhawa SCHARP, Fred Hutch
Laboratory protocol operations manager	On Ho HVTN Laboratory Program, Fred Hutch	*Clinical data manager*	Kris Donaty SCHARP, Fred Hutch
Regulatory affairs associate	Meg Brandon HVTN Core, Fred Hutch	*Senior clinical data manager*	Gina Escamilla SCHARP, Fred Hutch
Clinic coordinator	Shonda Sumner Vanderbilt CRS	*DAIDS Project Officers*	Chris Butler DAIDS, NIAID
Community Advisory Board (CAB) members	David Long Vanderbilt CRS		Nandini Sane DAIDS, NIAID
	Jemal Shelton-Thompson Atlanta Hope Clinic CRS	*Protocol development manager*	Meg Trahey HVTN Core, Fred Hutch
Community engagement unit representative	Stephaun Wallace HVTN Core, Fred Hutch	*Technical editor*	Richa Chaturvedi HVTN Core, Fred Hutch
Community educator/recruiter	Vic Sorrell Vanderbilt CRS		

4 Background

4.1 Rationale for trial concept

An effective vaccine against HIV-1 infection remains an elusive goal (4) and will likely need to induce robust humoral and cellular immune responses in order to both reduce acquisition and control postinfection viremia (5, 6). To date, only four vaccine concepts have been tested in field trials (7-12) and only one vaccine regimen has shown efficacy in preventing HIV-1 infection (12). In RV144, an ALVAC *env*/*gag*/PR prime at 0, 1, 3, 6 months with an AIDSVAX B/E gp120 Env boost at 3 and 6 months was found to have modest overall vaccine efficacy of 31% in the modified intention-to-treat cohort (12). Subsequent detailed analyses of potential correlates of protection and risk found that Env-specific binding IgG antibodies directed against the V1V2 region were found to positively correlate with protection (13), although protection peaked soon after vaccination and then waned over several years (14).

The successful use of a protein boost following a heterologous priming vaccine in RV144 has renewed interest in development of Env proteins as a component of future HIV-1 vaccine regimens. However, the field has been hampered by difficulties in manufacturing Env proteins, as well as uncertainty in the choice of immunogens (15). It is, therefore, quite likely that multiple different Env proteins will need to be tested in an iterative fashion, potentially both alone and as part of prime-boost combinations (16).

Furthermore, designing a vaccine regimen which can lead to induction of broadly neutralizing antibodies (bnAbs) has been a significant challenge for the field (17-19). Results thus far have mostly been limited to activity against easily-neutralized Tier 1 viruses (for example, HVTN 073E (20) and HVTN 083(21)) although some activity against more representative Tier 2 viruses was seen in HVTN 205 (22). Amongst the reasons why eliciting bnAbs has proven such a challenge include the trimeric conformational structure of Env, molecular mimicry of host antigens by conserved viral epitopes, as well as the atypical B cell maturation pathways and complex somatic mutations in immunoglobulin variable domains which may be required (23-26). If frequent and sequential immunization with serial Env proteins is necessary to direct B cell somatic mutation toward bnAb production in a step-wise fashion (27, 28), a hypothesis being tested in HVTN 115, then a very large number of Env proteins will need to be synthesized and tested in phase 1 studies in the near future.

One approach to shortening the product development timeline could be the use of transiently transfected cell lines (29) to produce Env proteins (30). In contrast with the current practice of developing stably transfected cell lines in order to produce sufficient quantities of clinical-grade product (31), use of transiently transfected cell lines could reduce the time required by at least several months (32). This would allow novel immunogens to enter phase 1 testing more quickly, thereby enabling faster iterative testing of more prime-boost regimens in order to

choose candidate regimens for efficacy trials (16). First, however, we propose that Env proteins produced by transiently transfected cell lines be tested in vivo to demonstrate that they have comparable safety and immunogenicity to Env proteins produced by stably transfected cell lines.

This study will use a clade C HIV-1 gp120 envelope protein (CH505TF gp120) adjuvanted with GLA-SE as the immunogen. This protein, produced via stably transfected cells, with GLA-SE, is also being tested in HVTN 115 (see Section 4.9.1). CH505TF gp120 produced by transient transfection has not yet been tested in a clinical trial, and therefore, this will serve as the first-in-human study for the protein produced by this method. The use of a gp120 Env has several potential advantages: 1) immunogenicity is related to binding affinity to B-cell receptors (BCRs) on the responding B cells (33, 34); 2) gp120 Env binds with high affinity to the germline unmutated common ancestor (UCA) antibody of the CH103-like bnAb lineage and binds with high affinities to other bnAb lineage intermediates; and 3) the exclusion of gp41 avoids stimulating non-neutralizing antibody responses to gp41 epitopes. This trial will allow direct comparison of an Env protein produced by two different methodologies and has the potential to greatly accelerate HIV-1 vaccine development.

4.2 Stable CH505TF gp120

The Duke Human Vaccine Institute (DHVI) developed the transmitted/founder CH505 Env (CH505TF gp120) vaccine in collaboration with NIAID as part of the B cell lineage approach to develop bnAbs (27, 28). CH505TF gp120 is a recombinant HIV-1 gp120 clade C Env protein with an N-terminal deletion that facilitates production by decreasing protein dimer formation and increasing production yield (35). This envelope sequence was derived from an African clade C transmitted founder virus CH505-infected individual (36). The Stable CH505TF gp120 was produced via stable transfection of a CHO-DG44 cell line and is also being tested in HVTN 115 (see Section 4.9.1). The Stable CH505TF gp120 will be mixed with GLA-SE (glucopyranosyl lipid A in a stable emulsion [oil-in-water emulsion containing squalene]) manufactured by the Infectious Disease Research Institute (IDRI).

4.3 Transient CH505TF gp120

The Transient CH505TF gp120 amino acid (aa) sequence is identical to the Stable CH505TF gp120. Transient transfection was achieved by electroporation with post-transfection scale up of suspension cultures to a bioreactor. CHO-DG44 cells did not recover from the transient transfection procedure as well as CHO-S cells; therefore, CHO-S cells were chosen to produce the Transient gp120. The purification process was similar to the stably expressed protein. As with the Stable CH505TF, the Transient CH505TF gp120 will be mixed with GLA-SE manufactured by IDRI.

4.4 Biochemical and biophysical equivalency of Stable and Transient CH505TF gp120

Bulk drug substance (BDS) batches of both Stable and Transient CH505TF gp120 proteins produced from CHO cells were purified by KBI Biopharma using multimodal and ion-exchange chromatography. The two products were compared by a series of biochemical and biophysical assays. Both forms (stable and transient) of CH505TF gp120 were monomeric by size exclusion chromatography (SEC) analysis (Figure 4-1) and showed similar migration on SDS-PAGE that was consistent with that of a 120kDa protein band (Figure 4-2). Neither form of CH505TF gp120 showed any detectable proteolytically cleaved fragment by SDS-PAGE under reducing or non-reducing conditions, and no clearly distinct fragment was detected by Western Blot analysis.

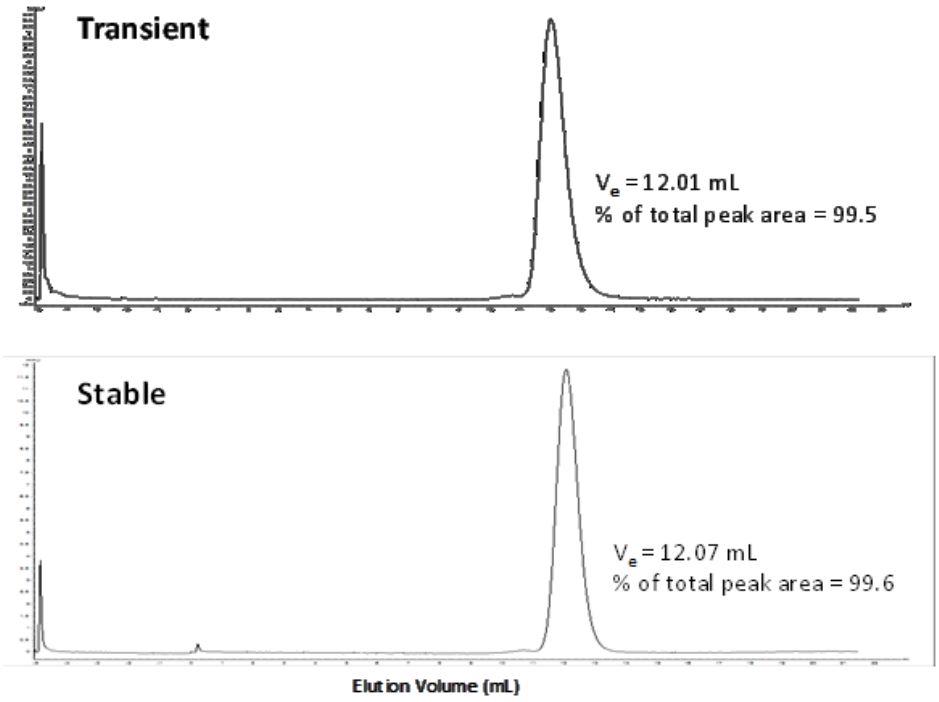

Figure 4-1 Size exclusion chromatography (SEC) analysis on a Superdex S200 increase (GE Healthcare) column confirms monomeric gp120 proteins with elution volumes (Ve) of 12.01 and 12.07 mL for transient and stable respectively. Both forms of gp120 proteins were about 99% monomeric.

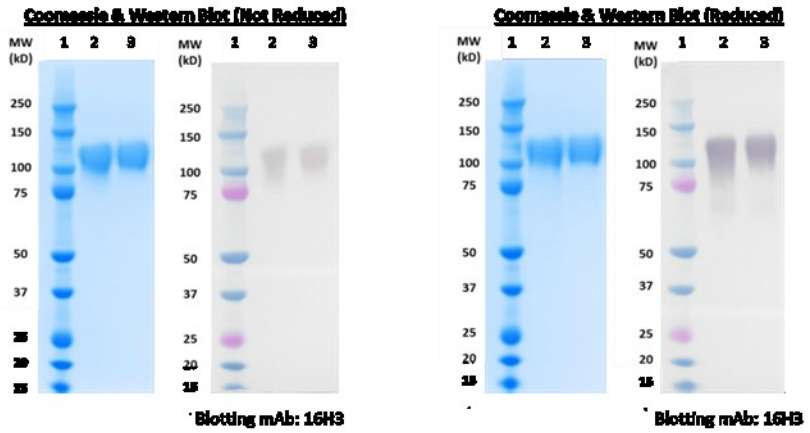

Figure 4-2 SDS-PAGE analysis of CH505TF gp120 produced by transient transfection and stable transfection. Western blots were developed using the gp120 monoclonal antibody 16H3.Lane 1 = MW markers, Lane 2 = Purified BDS of CH505TF from transiently expressed CHO-S cells, Lane 3 = Purified BDS of CH505TF from stable CHO-DG44 cell line.

The monodispersity of the two protein forms was also assessed by dynamic light scattering (Figure 4-3), which showed a complete absence of dimer or higher order oligomers. Not unlike the stable line produced CH505TF gp120, the transiently produced CH505TF gp120 gave a differential scanning calorimetry (DSC) thermal melting profile (Figure 4-4) with two resolved transition T_m (melting temperature) peaks (Tm_1/Tm_2 = 57.2/64.0 and 57.4/64.8ºC for transient and stable respectively), indicating that both forms of the proteins adopted a similar folded state.

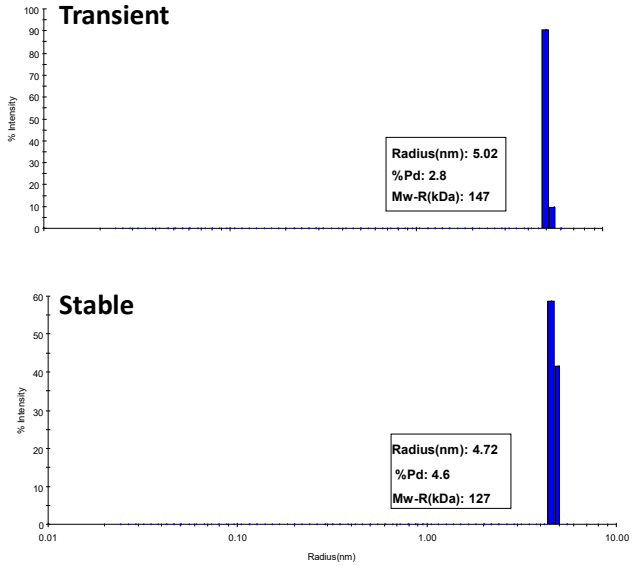

Figure 4-3 Dynamic light scattering analysis shows the absence of dimer or higher-order oligomers

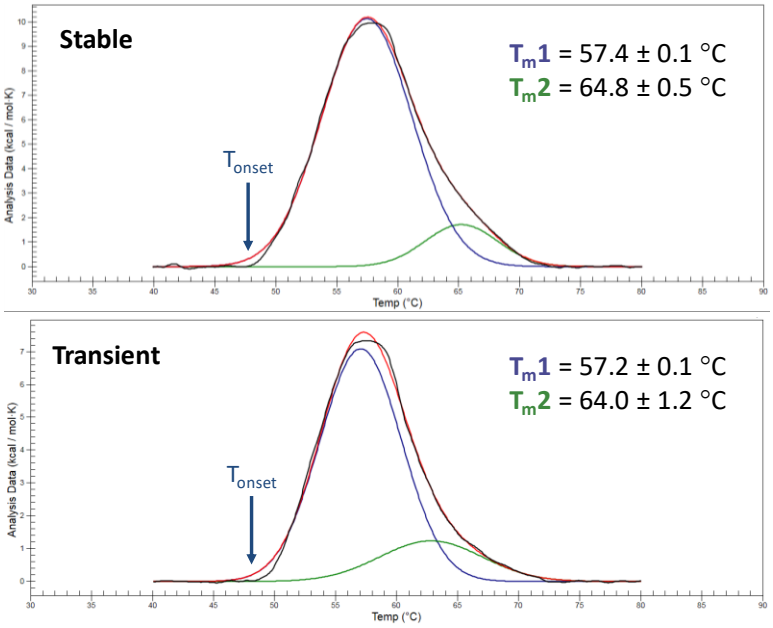

Figure 4-4 Differential Scanning Calorimetry (DSC) shows a similar unfolding profile with similar on-set and Tm values for stable and transient CH505TF gp120.

The antigenic signature of the transient gp120 was identical to its stable protein counterpart, with both gp120 proteins binding to each UCA, the intermediate IA3 as well as to the mature CH106 monoclonal antibody (mAb) of the CD4 binding site (CD4-BS) bnAb lineage (data not shown). No difference was observed in the affinities of either UCA (K_d = 489.5 and 491.4 nM for transient and stable respectively) or CH106 (K_d = 9.7 and 9.7 nM for transient and stable respectively) binding to the two protein forms (Table 4-1). The relative proportion of bnAb CH106-reactive fraction present in both stable and transient preparations when measured by isothermal titration calorimetry (ITC) analysis (stoichiometry n values) was similar (~ 60% active) (Figure 4-5). The closeness in values of CH106 affinities and enthalpy changes (ΔH) indicated that the binding of both the stable line produced and the transiently produced CH505TF gp120 follows a similar thermodynamic mechanism when binding to the CD4-BS bnAb. Thus, CH505TF gp120 produced by transient transfection was comparable to the CH505TF gp120 protein produced by stably transfected cells with respect to its biochemical/biophysical properties as well as its antigenicity for binding to CH013 lineage antibodies.

Table 4-1 Surface Plasmon Resonance (SPR) kinetic rates and dissociation constants (Kd) for binding of UCA and CH106 mAbs to CH505TF gp120

CH505 gp120	Unit	CH103 UCA	CH106
Reference gp120*:	k_a ($M^{-1}s^{-1}$)	2.06±0.07	0.87±0.07
CH505TF_D8gp120/293F	k_d (s^{-1})	102.02±5.18	0.55±0.06
Lot: 160226PPF 26Feb2016	K_d (nM)	496.2±17.8	6.3±0.2
Transient gp120:16-144-0515			
	k_a ($M^{-1}s^{-1}$)	2.08±0.05	0.75±0.05
Purified BDS of CH505TF from transiently expressed CHO-S cells	k_d (s^{-1})	101.76±8.18	0.75±0.06
	K_d (nM)	489.5±28.0	9.7±0.2
Batch# 144D16-01 Lot: 162340			
Stable gp120:15-144-0406			
	k_a ($M^{-1}s^{-1}$)	2.06±0.17	0.86±0.06
Purified BDS of CH505TF from stable cell line	k_d (s^{-1})	101.71±12.98	0.83±0.07
Batch# 144A15-02 Lot: 150769	K_d (nM)	491.4±31.8	9.7±0.3

*Reference CH505TF gp120 was produced in 293T cells and purified by lectin (GLN) affinity chromatography.

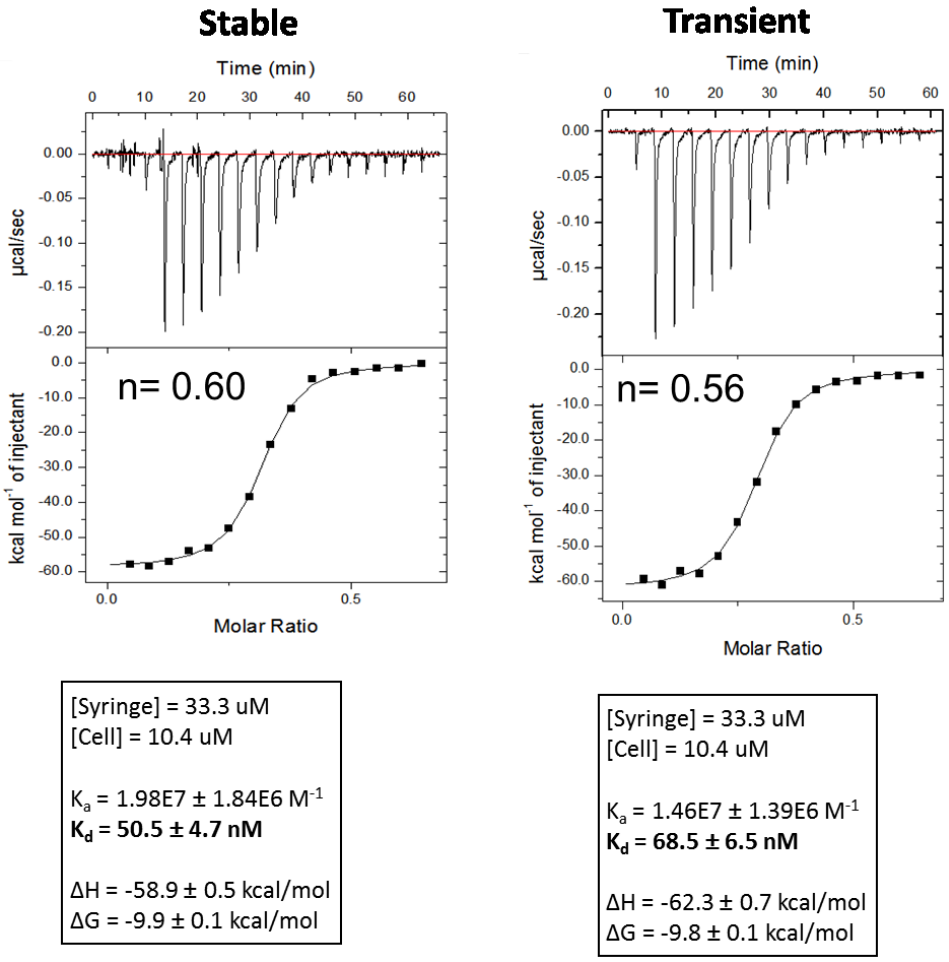

Figure 4-5 Isothermal titration calorimetry (ITC) analysis of CH106 binding to CH505TF gp120 show similar stoichiometry (n) and thermodynamic profile for stable versus transiently produced proteins.

4.5 Trial design rationale

This is a double-blind, randomized clinical trial, which will compare the safety and immunogenicity of a CH505TF gp120 produced via stably transfected cell lines compared with production via transiently transfected cell line. Fifteen healthy, HIV-1–uninfected adults will be enrolled into each group, vaccinated at months 0, 2, and 6, and followed for a total of 12 months. The design of this comparative study is intended to allow rapid assessment of the comparability of the Env proteins in terms of safety, tolerability, and immunogenicity. It is likely that antibody responses to the Env proteins will peak after the 3rd injection given at month 6. Assessments of humoral immune responses are planned at early, peak, plateau, and late timepoints by analyzing binding to a panel of Env antigens using the binding antibody multiplex assay (BAMA). From an immunogenicity perspective, this study design will allow us to assess both magnitude and breadth of humoral immune responses as well as understand in detail the kinetics of the antibody responses.

The overarching goal of this study is to demonstrate whether immunization with Env protein produced by transiently transfected cells is as safe and immunogenic as immunization with Env produced by stably transfected cells. While past vaccine trials of Env proteins (Envs) have used Envs made by stable transfection, much of the early animal research is performed using Envs produced by transient transfection. Envs made by both approaches have been safe and immunogenic in animal studies, and are analytically similar (Section 4.4), but HIV Envs made by transient transfection have not yet been tested in clinical trials. By directly comparing CH505TF gp120 produced by transiently transfected cells with CH505TF gp120 produced by stably transfected cells this study has the potential to enable future clinical trials with novel Env immunogens to launch much faster.

4.5.1 Dose (amount and number)

Both the CH505TF gp120 produced by transiently transfected cells and the CH505TF gp120 produced by stably transfected cells will be given at a fixed dose of 100 mcg per injection. In HVTN 115 Part A, the Stable CH505TF gp120 will be tested at 20 mcg, 100 mcg, and 400 mcg to determine the optimal dose for Part B. The 100 mcg dose of CH505TF gp120 was chosen for this study as it is likely to be in the linear range in terms of antibody responses. The TLR4 agonist GLA-SE adjuvant will be admixed with all proteins. The total dose of GLA-SE will be 10 mcg (lipid A) at all timepoints. The 10 mcg dose of GLA-SE was selected based upon preclinical studies demonstrating safety (rabbits) and immunogenicity (guinea pigs and rhesus macaques) of the Stable CH505TF gp120 + GLA-SE vaccine (see Sections 4.7 and 4.8) and the established safety profile of the GLA-SE adjuvant in human clinical trials (see Section 4.9.2). Furthermore, the 10 mcg dose of GLA-SE is being used in HVTN 115 (see Section 4.9.1). All injections will be administered IM by needle and syringe.

4.5.2 Schedule

Vaccinations will occur at months 0, 2, and 6. These immunization intervals were chosen based on prior studies with different Env proteins and are likely to lead to high peak antibody titers and high humoral response rates after the third vaccination. In previous trials with adjuvanted protein vaccines, peak immunogenicity has been observed after 3 doses of the protein, while a prolonged rest period between the 2nd and 3rd vaccinations is thought to enhance antibody maturation.

4.6 Plans for future product development and testing

The Stable CH505TF gp120 vaccine is a component of the regimen being tested in HVTN 115, which represents the first clinical trial of administration of sequential Env proteins in an attempt to elicit CD4-binding site (CD4-BS) bnAbs. HVTN 115 is likely to be the first of a series of iterative clinical trials to optimize induction of bnAbs. The overarching goal of this study is to demonstrate whether Env protein production by transiently transfected cells is as safe and

immunogenic as production by stably transfected cells to enable future clinical trials with novel Env immunogens to launch much faster.

4.7 Preclinical safety study

Table 4-2 Summary of preclinical safety study

Study number	Product	Type of study	Animal	N/group	Dose groups	Route	Schedule
1726-031	Stable CH505TF	Toxicity	New Zealand White Rabbits	10 M, 10 F	Group 1: saline control Group 2: CH505TF + GLA-SE Group 3: DNA + CH505TF + GLA-SE Group 4: GLA-SE	IM	Days 1, 15, 29, 43, 57, 71, 85

4.7.1 Preclinical toxicology study of Stable CH505TF gp120 in rabbits

A toxicity study with Stable CH505TF gp120 in New Zealand White (NZW) rabbits was conducted in compliance with Good Laboratory Practices (GLP). Seven biweekly IM injections of 400 mcg CH505TF gp120 with 20 mcg GLA-SE adjuvant coadministered with or without a 4 mg DNA, or 20 mcg GLA-SE alone, to NZW rabbits for 13 weeks were well tolerated. Test article-related changes in dermal scores, clinical pathology parameters, and microscopic injection site findings were resolved/partially resolved and/or trending toward recovery by the recovery necropsy, and none of the test article-related changes were deemed adverse. A more detailed description of the toxicity study can be found in the Investigator's Brochure (IB).

4.7.2 Preclinical toxicology study of Transient CH505TF gp120

Toxicity studies with Transient CH505TF gp120 Env have not been done. As the amino acid sequence is identical between the Transient and Stable CH505TF gp120 Env proteins, a significant difference in toxicity is not expected.

In July 2017, a Briefing Package was sent to the FDA, in which results from release testing, biophysical and biochemical characterization, and antigenicity studies of Stable CH505TF and Transient CH505TF gp120 proteins were summarized. Results from these preclinical tests indicated that the two proteins were similar with respect to release testing and physicochemical characterization. Both proteins demonstrated the expected binding to CH103 lineage antibodies that target the CD4 binding site; showing weak affinity binding to UCA and higher affinity binding to both an intermediate lineage antibody (IA3.2) and the mature CH106 bnAb. In addition, a subset of preclinical safety and immunogenicity studies conducted with the Stable CH505TF variant were presented in support of the clinical safety experience with this gp120 protein. DAIDS proposed that the combination of the physicochemical data and clinical

safety data presented are sufficient and an additional GLP toxicology study of the Transient CH505TF would not provide additional useful information on the safety of the Transient CH505TF gp120 protein, and was not being planned. In addition, clinical safety data from the ongoing study of the stably produced CH505TF protein will be available prior to the initiation of the comparative study described here. The FDA concurred that no additional toxicology studies or pre-IND were required.

4.8 Preclinical immunogenicity studies

Table 4-3 Summary of preclinical immunogenicity studies

Study number	Product	Animal	N	Regimen groups	Route	Schedule (weeks)	Assay
501	CH505TF gp120 Env with GLA-SE	Guinea pigs	4 per group	1 mcg CH505TF only 1 mcg CH505TF, 5 mcg GLA-SE 1 mcg CH505TF, 10 mcg GLA-SE 1 mcg CH505TF, 25 mcg GLA-SE 5 mcg CH505TF only 5 mcg CH505TF, 5 mcg GLA-SE 5 mcg CH505TF, 10 mcg GLA-SE 5 mcg CH505TF, 25 mcg GLA-SE 50 mcg CH505TF only 50 mcg CH505TF, 5 mcg GLA-SE 50 mcg CH505TF, 10 mcg GLA-SE 50 mcg CH505TF, 25 mcg GLA-SE	IM	0, 3, 6, 9, 12	Ab binding
NHP 79	EnvSeq-1 gp120 Env with GLA-SE	Rhesus Macaques	4 per group	100 mcg CH505TF only 100 mcg CH505 sequential Envs 100 mcg CH505 additive Envs	IM	0, 6, 12, 19, 24, 57	NAb, binding Ab, blocking Ab
NHP 106	CH505TF gp120 Env with GLA-SE	Rhesus Macaques	4 per group	5 mcg CH505TF Env 20 mcg CH505TF Env 100 mcg CH505TF Env 300 mcg CH505TF Env 600 mcg CH505TF Env	IM	0, 4, 12, 29, 37	NAb, binding Ab, blocking Ab
04	Stable CH505TF gp120 with GLA-SE Transient CH505TF gp120 with GLA-SE	Balb/C mice	7 per group	1 mcg Stable CH505TF, 5 mcg GLA-SE 10 mcg Stable CH505TF, 5 mcg GLA-SE 25 mcg Stable CH505TF, 5 mcg GLA-SE 1 mcg Transient CH505TF, 5 mcg GLA-SE 10 mcg Transient CH505TF, 5 mcg GLA-SE 25 mcg Transient CH505TF, 5 mcg GLA-SE	IM	0, 2, 4,	Ab binding, blocking Ab

The CH505TF gp120 used in the initial animal studies (guinea pig 501 and NHP 79) was generated in transiently-transfected 293 cells. The 293-produced CH505TF gp120 has a different glycosylation profile than that of the CHO-produced protein used for the rabbit toxicology study, mouse immunogenicity, and for the nonhuman primate (NHP) dose response study (NHP 106).

4.8.1 Immunogenicity of CH505-derived gp120 envelopes with GLA-SE in guinea pigs

In a guinea pig study, the GLA-SE adjuvant was necessary for optimal immune responses to gp120 at all doses (Figure 4-6).

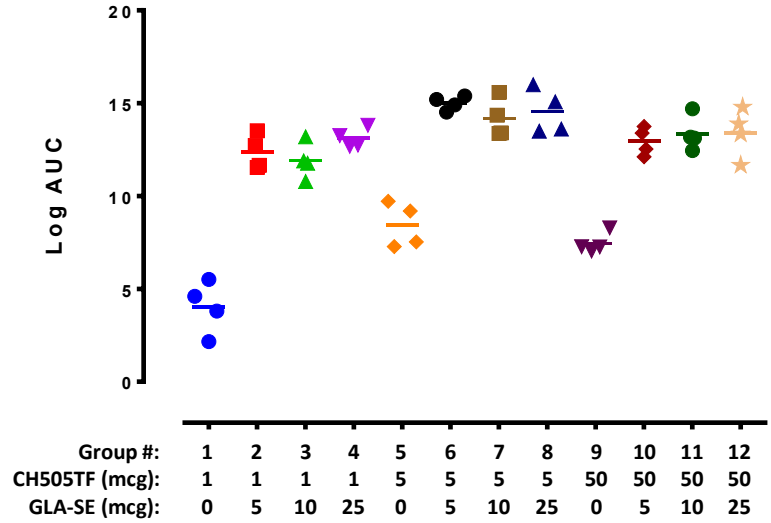

Figure 4-6 GLA-SE enhanced immunogenicity of CH505TF gp120 protein in guinea pigs. Binding antibodies from guinea pigs immunized with varying doses of CH505TF gp120 and varying amounts of GLA-SE were measured by enzyme-linked immunosorbent assay (ELISA). The data were used to calculate the log-transformed area under the curve (AUC) as shown on the y-axis. CH505TF gp120 was immunogenic at all doses. Groups 1, 5 and 9 received no GLA-SE and had significantly less anti-gp120 antibodies than the groups with 5 mcg (Groups 2, 6 and 10), 10 mcg (Groups 3, 7, and 11) or 25 mcg (Groups 4, 8, and 12) of GLA-SE. Moreover, there was no difference between the three GLA-SE doses (statistical analysis not shown).

4.8.2 Immunogenicity of CH505-derived gp120 Envelopes, study NHP 79

The EnvSeq-1 immunogens consist of four gp120 proteins derived from CH505: CH505TF, CH505w53, CH505w78, and CH505w100. These proteins were administered to 3 groups of four rhesus macaques (NHP 79) with the GLA-SE adjuvant: 1) CH505TF Env gp120 alone; 2) the Envs given in a sequential regimen (CH505TF, CH505w53, CH505w78, and CH505w100); and 3) an additive-immunization regimen consisting of CH505TF gp120 in combination with the evolved Env variants (CH505TF, then CH505TF + CH505w53, then CH505TF + CH505w53 + CH505w78, then CH505TF + CH505w53 + CH505w78 + CH505w100). These Envs were research grade products made by transient transfection of 293 cells and have different glycosylation profiles than the CHO-produced CH505TF gp120s to be used in this clinical trial. This study demonstrates the proof of concept of using sequential Env variants in NHPs.

The CH505 gp120 Env derivatives (including CH505TF) were found to be immunogenic (Table 4-4). An important readout in this study was differential binding to the CD4-BS of the envelope protein. This assay detects antibodies which bind to wild type CH505 Env gp120 but not to CH505 with a deletion of isoleucine at aa position 371 (CH505 Env IΔ371 gp120), indicating CD4-BS

recognition which is a key trait of the CH103-like bnAbs. The data from the NHP 79 study suggest that triggering of UCAs of lineages capable of binding HIV Envs with wild type sequences without further evolution into bnAbs can occur. In this study of 12 monkeys, 11/12 monkeys had differential binding antibodies isolated but overall the Env differential binding antibodies were subdominant and comprised only about 15% of the total activity of the antibody response, which is consistent with development of bnAbs in HIV-infected individuals.

Table 4-4 CH505 Env gp120 derivatives are immunogenic in rhesus macaques. Plasma was screened for neutralization of HIV-1 isolates via the TZM-bl assay. ID_{50} positivity cutoff was ≥20 or 3x > background neutralization of MuLV. *40-49% virus neutralization; less than 50% required to generate an ID_{50} value.

ID50 reciprocal dilutions	<20	20-100	101-1,000	1,001-10,000

Vaccine groups	Animal ID	Neutralization (ID50)							
		CH505 (Tier 2)	CH505.w4.3 (Tier 1b)	C.MW965 (Tier 1)	B.SF162 (Tier 1)	B.SS1196 (Tier 1b)	C.6644 (Tier 1b)	D.57128 (Tier 2)	MuLV
Group 1 – CH505 T/F Env alone	17	<20	359	958	20	<20	46	<20	<20
	18	<20	577	138	48	<20	<20	<20	<20
	19	<20	68	81	<20	<20	<20	<20	<20
	20	<20	1453	3470	302	49	67	<20*	<20
Group 4 – CH505 Sequential Envs	21	<20	990	1775	49	24	37	<20*	<20
	22	<20	539	335	<20	48	36	22	21
	23	<20	293	293	29	<20	<20	<20*	<20
	24	<20	1908	1255	78	<20	34	22	<20
Group 5 - CH505 Additive Envs	25	<20	296	469	34	<20	<20	<20	<20
	26	<20	341	264	47	24	26	<20*	<20
	27	<20	470	318	55	<20	25	<20	<20
	28	<20	130	329	<20	<20	<20	<20	<20

4.8.3 Immunogenicity of Stable CH505TF gp120, study NHP 106

A dose ranging study was performed in rhesus macaques using 5 to 600 mcg of Env CH505TF gp120 (produced by stably transfected CHO-DG44 cells) along with 25 mcg GLA-SE with each dose administered 5 times. Immunogenicity was demonstrated at all dose levels and no adverse reactions were observed. Env binding antibody (Figure 4-7) and CD4-BS antibody (Figure 4-8) levels were determined and the CH505 TF gp120 was found to be immunogenic after 2 immunizations. All dose levels gave similar binding responses. When we assessed the frequency of memory B cells that bind antigen probes in a CD4-BS differential manner (called differential binding memory B cells), all animals in the 20, 100, 300, and 600 mcg protein dose groups demonstrated differential binding after 3 injections (Figure 4-9).

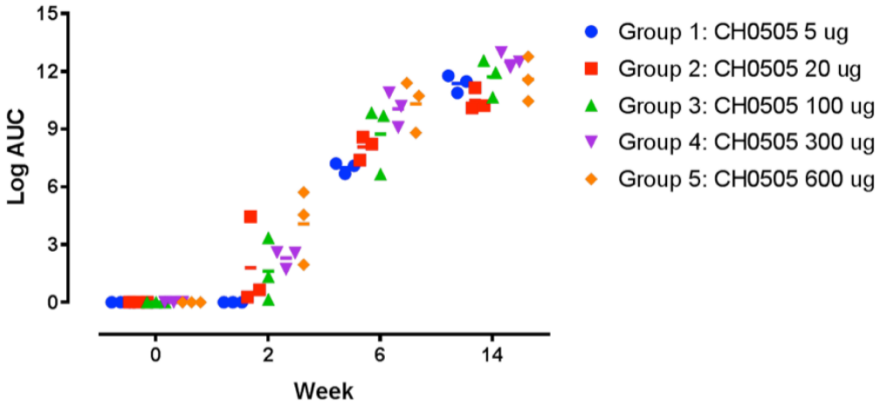

Figure 4-7 Binding of Immunized NHP 106 Plasma to CH505TF gp120. Each data point represents a single animal. Animals were immunized with the indicated dose at weeks 0, 4 and 12. Note that the x-axis shows bleed time. Bleed 0 was performed before immunization and subsequent bleeds were performed 2 weeks after each respective immunization. No animals had binding antibodies prior to immunization; binding was detected in all animals after the second immunization. After the third immunization, binding antibodies were similar among all groups. While all doses gave a similar binding response, the higher doses of 300 and 600 mcg gave earlier responses and trended to higher responses compared to the lower doses. No additional rise in antibody levels was observed after the fourth or fifth immunizations (data not shown)

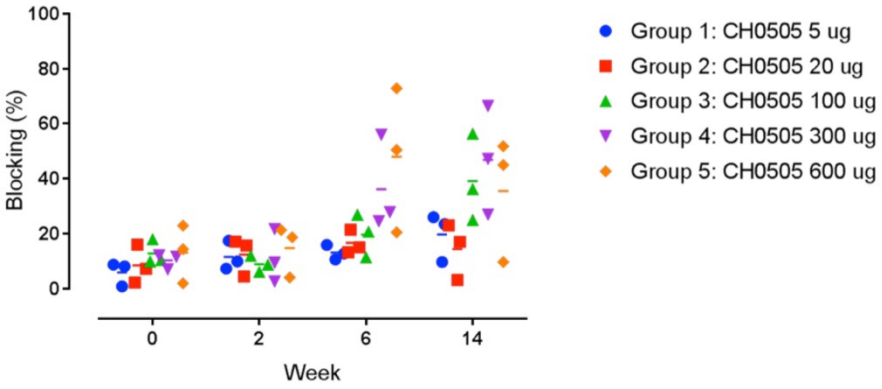

Figure 4-8 Inhibition of CD4 binding by NHP 106 plasma after immunization with 5 different doses of CH505TF gp120. Each data point represents a single animal. Animals were immunized with the indicated dose at weeks 0, 4 and 12. Note that the x-axis shows bleed time. Bleed 0 was performed before immunization and subsequent bleeds were performed 2 weeks after each respective immunization. The ability of plasma antibody to block the binding of CD4bs mAb CH106 to heterologous B.63521 gp120 was quantified by ELISA. Blocking antibodies were detectable in the high dose groups after the second immunization and increased in Group 3 after the third immunization.

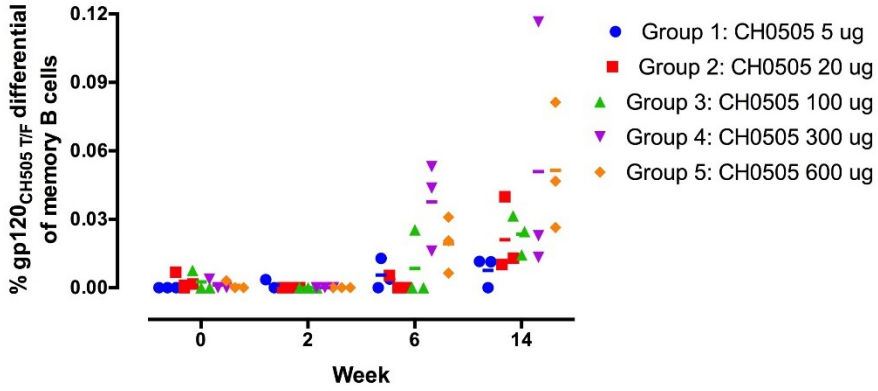

Figure 4-9 Percentage of differential binding memory B cells. Peripheral blood mononuclear cells (PBMC) from immunized macaques were assayed to determine the frequency of memory B cells that bind to CH505TF gp120 but not to CH505TF gp120 ΔI371 that disrupts the CD4 BS. Each data point represents a single animal. Animals were immunized at the indicated dose at weeks 0, 4 and 12. Note that the x-axis shows bleed time. Bleed 0 was performed before immunization and subsequent bleeds were performed 2 weeks after each respective immunization. Data show a pattern of increased differential binding memory B cell induction with increasing dose starting after two immunizations and increasing after a third immunization.

4.8.4 Immunogenicity of Stable CH505TF gp120 and Transient CH505TF gp120 in Balb/C mice, study 04

Immune responses from the Transient and Stable CH505TF gp120 vaccines were evaluated in a preclinical immunogenicity study conducted by the Barton Haynes Laboratory at the Duke Human Vaccine Institute (DHVI). The immunogenicity of each vaccine was evaluated in female BALB/c mice after 2 or 3 IM immunizations with the respective protein adjuvanted with 5 mcg of GLA-SE per mouse dose. Six groups of 7 female BALB/c mice were immunized every 2 weeks for a total of 3 immunizations with each respective vaccine. Pre-bleeds/sera were taken 2 weeks prior to and on the day of immunization 1 (day 0). Post bleeds were collected 1 week after each immunization.

The immunogenicity of each form of recombinant gp120 was evaluated by ELISA for the ability of vaccine to induce serum antibodies to bind recombinant Env gp120 (Figure 4-10 and Figure 4-11) (36). The vaccine-induced antibodies' ability to block the binding of the CD4 binding site neutralizing antibody to recombinant gp120 was also evaluated by ELISA using methods described in reference (35). Groups were compared by Exact Wilcoxon test (also called Wilcoxon-Mann-Whitney) with the Benjamini-Hochberg (1995) correction for multiple testing (see Figure 4-12 and Figure 4-13).

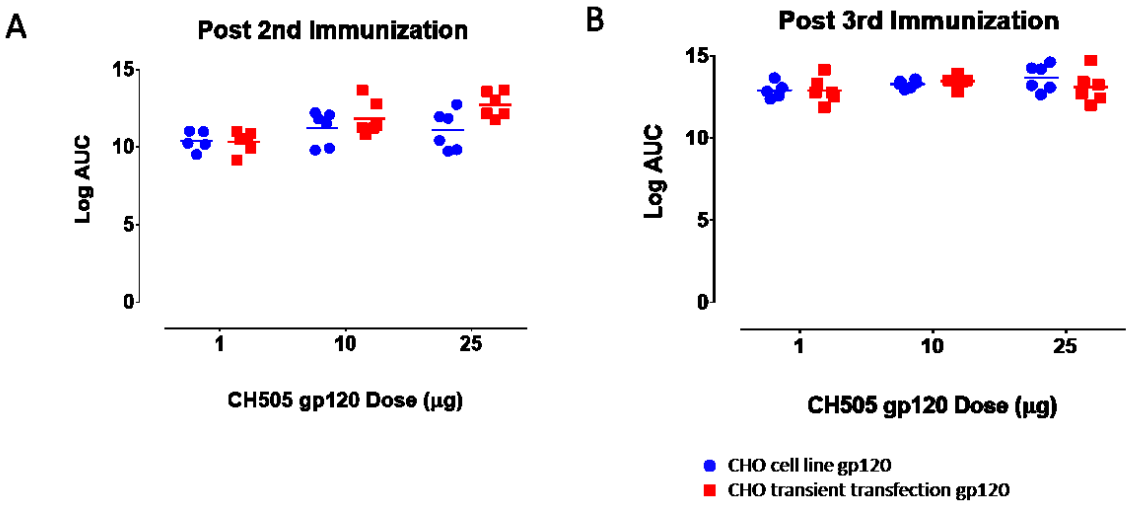

Figure 4-10 The binding of serum antibody to coating antigen CH505 gp120 reference produced in 293F cells

Figure 4-10A shows the binding of serum antibodies induced by the Stable CH505TF (blue circles) and the Transient CH505TF (red squares) to a reference coating antigen CH505 gp120, produced in 293F cells. The data show equivalent binding of antibodies induced by either vaccine to the reference gp120, with a slight trend of better binding with 10 and 25 mcg doses after the second immunization by serum antibodies induced by the Transient CH505TF Env. However, this difference was not statistically significant. Figure 4-10B shows the same analysis after the third immunization and again showed no difference in the binding of the antibodies induced by the two proteins.

Figure 4-11 shows the time course of serum antibody binding to the indicated coating Env protein listed over each graph of antibodies induced by the highest dose (25 mcg) of Stable CH505TF gp120 Env (blue dots) or Transient CH505TF gp120 Env (red squares). Binding of immune serum to Stable CH505TF is shown in Panel A and binding to Transient CH505TF is shown in Panel B. The engineered resurfaced core 3 (RSC3) protein was used to detect antibodies antigenically related to CD4-binding site binding, and results are shown in Panel C (37). Panel D shows binding to the heterologous gp120 YU2. YU2 gp120 is CD4-binding site knock-out mutant lacking variable regions V1, V2, and V3 and truncated at the N- and C-terminal regions; binding to YU2 gp120 indicates serum antibodies directed to the gp120 scaffold (37). Panel E displays binding to the CH505TF V2 peptide (GMKNCSFNITTELRDKREKKNALFYKLDIVQLDGNSSQYRLIN). Lastly, Panel F demonstrates binding to CH505 V3 peptide (TRPNNKTRTSIRIGPGQAFYATGQVIGDIREAY). These data show that the binding profile of antibodies induced by either the stable cell line gp120 or the transiently transfected-produced gp120 was near identical. With the data in Panels A, B, D and F, there was a slight but statistically non-significant trend to the transiently transfected-produced material to be better as an immunogen.

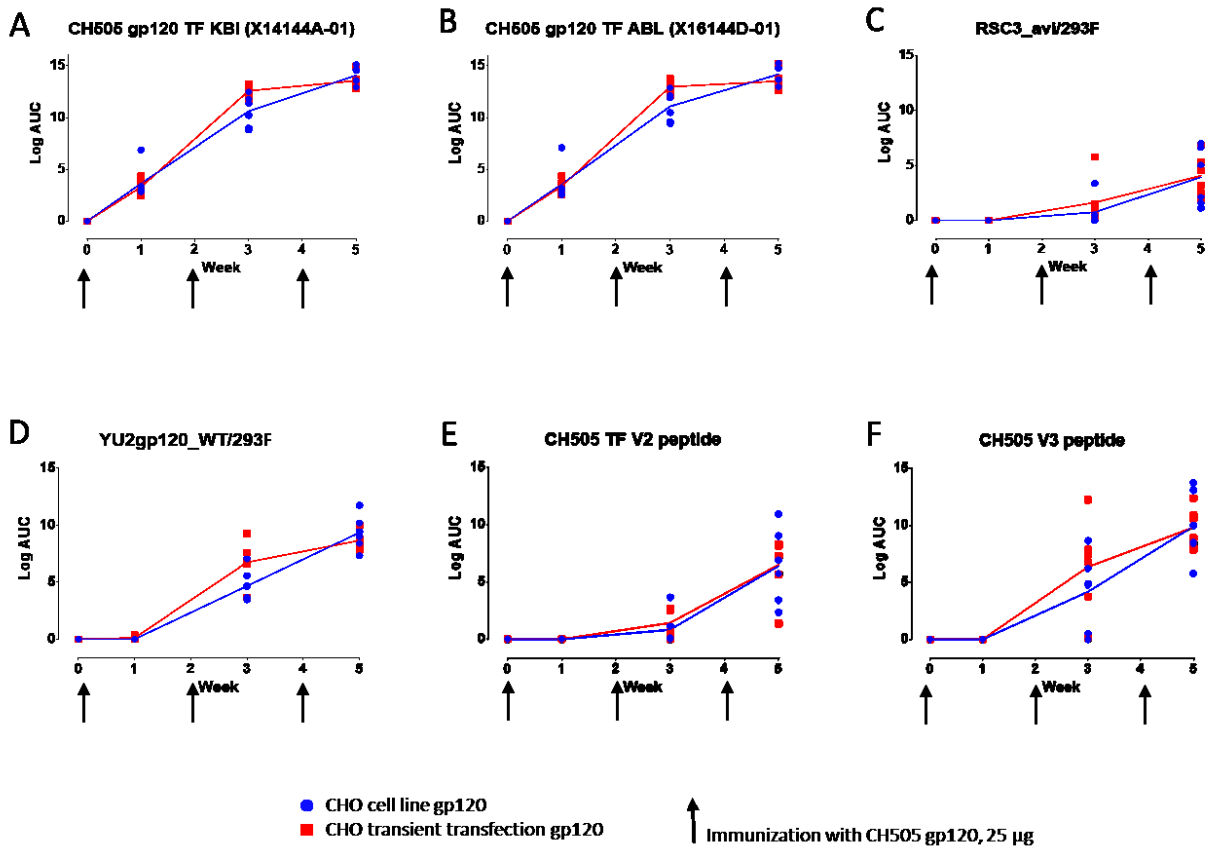

Figure 4-11 Time course of serum antibodies to the indicated coating Env protein induced by 25 mcg dose of immunogen

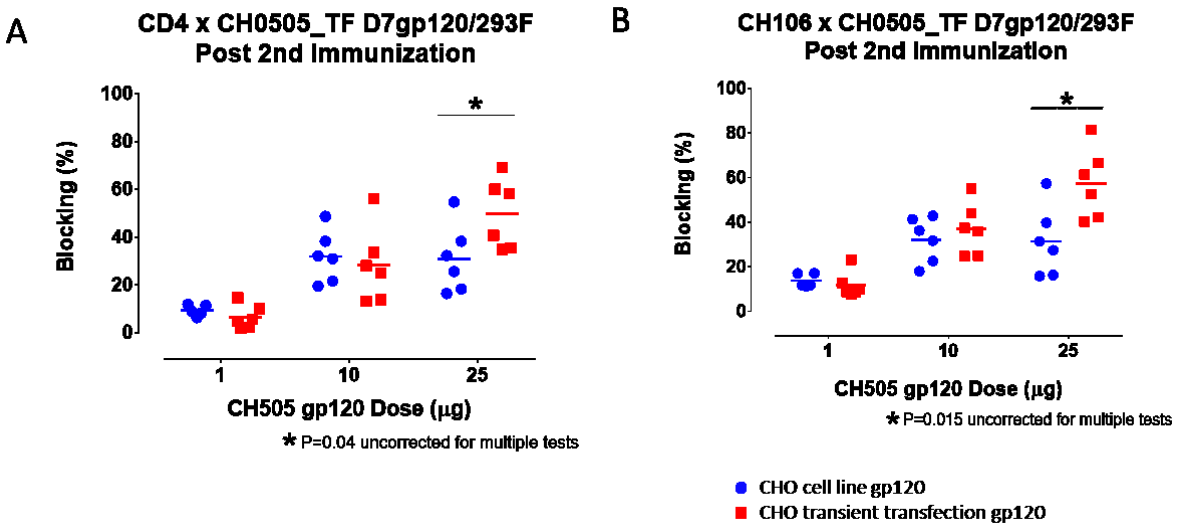

Figure 4-12 Vaccine induced serum antibodies to block soluble (s) CD4 or CH106 bnAb binding to the reference CH505 gp120

Figure 4-12 and Figure 4-13 show the results of the vaccine-induced antibodies to block either sCD4 or CH106 neutralizing antibody binding to reference CH505 Env gp120. Figure 4-12A shows the dose response of induced serum antibodies generated by vaccination with either Stable CH505 (blue dots) or Transient CH5050 gp120 (red squares). Data show that after the second immunization (Figure 4-12A), there was a significant improvement in blocking of sCD4 binding to gp120 with transiently transfected Env-immunized serum compared to stable cell line-produced gp120-immunized serum. A similar difference was seen after the second immunization for ability of serum to block the binding of the broadly neutralizing antibody (bnAb) CH106 to Env gp120 (Figure 4-12B).

Figure 4-13 shows the time course of blocking in the sCD4 blocking assay (Panel A) and the CH106 blocking assay (Panel B) and shows slight (not statistically significant) trend of increased blocking by the transient gp120-induced antibodies after the second immunization but no difference in blocking after the 3rd immunization.

The immunogenicity of each form of the recombinant gp120 was near identical in all performed assays. The Transient CH505TF gp120 induced slightly better CD4 binding site antibodies than the Stable CH505TF. Thus, the two proteins were highly comparable in their immunogenicity in BALB/c mice, as measured by Env-reactive antibodies, with a trend toward higher induction of CD4 binding site targeted antibodies by Transient produced gp120.

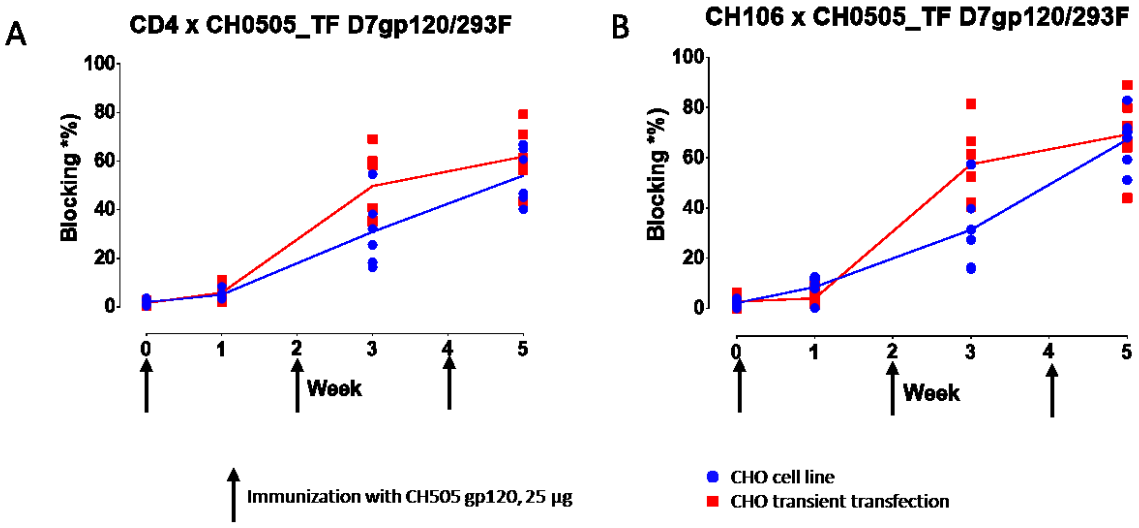

Figure 4-13 Time course of serum antibodies to block sCD4 and CH106 to the reference CH505 gp120

4.9 Clinical studies

4.9.1 Clinical studies of Stable CH505TF gp120 vaccine

The Stable CH505TF gp120 is being evaluated in HVTN 115. In the dose ranging portion of that clinical trial (HVTN 115 Part A) safety and immunogenicity data will be collected to inform the protein dose for the second part of that study. HVTN 115 Part A reached full enrollment with 42 participants in May 2018. As of June 25, 2018, there has been one case of grade 3 erythema/induration with grade 2 cellulitis after the second vaccination. All other reactogenicity events have been mild-moderate and vaccinations have been well tolerated.

There is extensive clinical trial experience with other gp120 Env proteins evaluated either alone or in combination with various prime or boost regimens. The AIDS Vaccine Evaluation Group (AVEG) conducted an analysis of safety data from over 15 clinical trials of gp120 and gp160 proteins administered to over 500 individuals demonstrating that overall, HIV Env proteins at doses up to 640 mcg were well tolerated. The majority of the local and systemic reactions were deemed associated with the adjuvant components of the vaccine rather than the Env proteins themselves (38).

A monovalent subtype B and bivalent subtype B/E (CRF01_AE) recombinant gp120 HIV-1 vaccine (AIDSVAX B/E) was evaluated in an efficacy study conducted in over 2500 injection drug users in Thailand. A total of 600 mcg of AIDSVAX B/E was administered with alum as an adjuvant. The most commonly reported adverse event (AE) was tenderness at the injection site (71% of vaccine recipients versus 66% of placebo recipients), which did not increase with subsequent injections. There were no differences between vaccine and placebo recipients with respect to the number of serious AEs (SAEs) (39).

The RV144 study evaluated the same gp120 vaccine in a heterologous prime-boost vaccination regimen consisting of a recombinant canarypox vector expressing gag, PR, and env (ALVAC-HIV; vCP1521) followed by the gp120 protein boost. Over 8000 participants received multiple combined doses of 600 mcg of gp120 in combination with ALVAC-HIV (12). Local and systemic reactogenicity noted after the gp120 protein (AIDSVAX B/E) was mostly mild with very few SAEs reported (40).

Prior clinical experience comparing various doses of gp120 and gp160 Env proteins has not identified significant differences in the safety profile when the protein dose was altered and adjuvant dose remained constant. For example, in a study evaluating AIDSVAX B/E gp120 at 100 mcg (N=31), 300 mcg (N=31) and 600 mcg (N=30) of the protein adjuvanted with alum, the majority (80%) of participants reported at least one reactogenicity event, most commonly injection site pain/tenderness, but all of the reactogenicity symptoms were mild to moderate and self-limited. Furthermore, although there were fewer reactogenicity events at the 100 mcg dose, the safety profile in the 300 mcg and 600 mcg groups was similar (41). A study of recombinant gp160 VaxSyn formulated with an alum

adjuvant compared two doses of 160 mcg (N=20) and 640 mcg (N=21) of the protein administered as 4 injections over a 12 month period. Local reactogenicity (injection site erythema/induration) was frequent but self-limited, lasted less than 48 hours, and the frequency of local reactogenicity was similar between the two dose groups. There were no significant differences in severe local or systemic reactions between the dose groups. Importantly, there were no significant differences in laboratory abnormalities (hepatic, hematologic and renal function) between the two different protein doses (42).

Taken together, the combined data from the large numbers of trial participants in these studies demonstrate that gp120 recombinant protein vaccines administered in combined doses of up to 600 mcg are immunogenic and well tolerated. There has been one recent case of anaphylaxis deemed related to the vaccine. There were no other unusual or serious vaccine-associated AEs reported.

4.9.2 Clinical studies of the GLA-SE adjuvant and protein combinations

GLA-SE is a synthetic TLR4 agonist formulated in a stable nano-emulsion of squalene oil and promotes a strong Th1-type immune response to vaccine antigens (43, 44). Although the Transient CH505TF gp120 protein in combination with GLA-SE has not been evaluated in humans to date, as summarized in Section 4.9.1, the Stable CH505TF gp120 is under evaluation in HVTN 115. In addition, there is considerable clinical trial experience with the GLA-SE adjuvant in combination with other antigens. These data are summarized below and in Table 4-5 and Table 4-6. Over 1100 individuals have received at least one dose of the GLA-SE adjuvant at doses ranging from 0.5 to 20 mcg with no significant safety concerns identified to date. Please see the IB for additional details of the clinical trials performed with GLA-SE.

Five studies have included the 10 mcg dose of the GLA-SE adjuvant proposed for this study. The first was an open-label phase 1 clinical trial conducted in Brazil with a Schistosoma mansoni antigen (Sm14) (45). Twenty healthy males received 3 IM doses of 50 mcg Sm14 + 10 mcg GLA-SE at one-month intervals. The vaccine was safe and generally well tolerated with no SAEs or Grade 4 AEs (45). Injection site pain was commonly reported (80%, 50%, and 41% after the first, second, and third dose, respectively), but generally mild and self-limited. There were no abnormalities in physical exams, serum chemistries, and hematology values that were considered related to study vaccine. Humoral and CD4+ T cell responses to Sm14 were reported (45).

The second clinical trial using the 10 mcg dose of GLA-SE is a recently completed phase 1, open-label evaluation of the safety, tolerability, and immunogenicity of a Leishmania vaccine (LEISH-F3) in combination with SLA-SE (second generation glucopyranosyl lipid A in stable oil-in-water emulsion) adjuvant compared to LEISH-F3 with GLA-SE in healthy adults (NCT02071758; Protocol IDRI-LVVPX-117). The SLA-SE adjuvant is a next generation TLR4 adjuvant formulation. Thirty-nine participants were randomized to 4 arms: high dose LEISH-F3 (20 mcg) and low dose SLA-SE (5 mcg); high dose LEISH-F3

and high dose GLA-SE adjuvant (10 mcg); low dose LEISH-F3 (5 mcg) and high dose GLA-SE adjuvant (10 mcg); and high dose LEISH-F3 and high dose SLA-SE adjuvant (10 mcg). Participants received 3 injections at one-month intervals. This study is complete. The LEISH-F3 + GLA-SE and LEISH-F3 + SLA-SE vaccines were safe and well tolerated in adult subjects. No deaths, no dose-limiting toxicities (DLTs), no Grade 3 or 4 AEs, no SAEs, and no AESIs occurred during the study. All study injection reactions were Grade 1 or Grade 2. The most frequently reported reactions were injection site tenderness/pain and fatigue.

Three other clinical trials are evaluating GLA-SE in oncology. Two ongoing trials are investigating GLA-SE alone as an immunotherapy and one trial tested GLA-SE in combination with a prostate cancer antigen. No data are currently available from these trials.

Clinical experience with GLA-SE as an adjuvant for other vaccines at doses ranging from 1 mcg to 5 mcg suggests that it is safe and well-tolerated. Treanor et al. tested an avian influenza hemagglutinin (H5) subunit vaccine at a range of doses with and without a fixed dose of GLA-SE (1 mcg) and reported mild to moderate injection site pain and/or tenderness in 50–70% of H5 + GLA-SE recipients, with myalgias and headaches reported by a minority (25-27%) of vaccinees. No other safety findings were noted and the GLA-SE adjuvant substantially increased the immunogenicity of the vaccine (46).

A recent phase 1 clinical trial of a respiratory syncytial virus (RSV) vaccine in older adults (≥ 60 years of age) found that a combination of the RSV fusion (F) protein at three different doses with 2.5 mcg of GLA-SE was safe, well-tolerated, and immunogenic. Compared with unadjuvanted vaccine, GLA-SE increased local reactogenicity, with 40-65% of subjects reporting mild-to-moderate, self-limited injection site pain and/or tenderness (47). No other safety concerns were reported. Immune responses were F protein dose-dependent, and the adjuvant enhanced both humoral and cellular immune responses (47). A follow-up study using a higher dose of F protein and three doses of GLA-SE has been completed (NCT02289820). The vaccine was safe, tolerable, and immunogenic and the data supported the selection of 120 mcg F protein /5 mcg of GLA-SE for further evaluation (48).

GLA-SE was also found to be safe and well-tolerated at doses of 2 mcg and 5 mcg in a phase 1 trial of LEISH-F3 given three times at one month intervals (49). Injection site pain and/or tenderness was quite common (90-100%) with fatigue noted by 40-60% of vaccinees receiving the adjuvanted product versus 33% of subjects who received unadjuvanted vaccine (49). The unadjuvanted LEISH-F3 was essentially non-immunogenic while antibody and cytokine responses were noted in vaccinees in both dose groups of GLA-SE (49).

GLA-SE at a 5 mcg dose has also been tested together with protein antigens in several other clinical trials which are included in Table 4-5 and Table 4-6.

Table 4-5 Completed clinical trials using IDRI GLA-SE adjuvant formulations in combination with other vaccines (as of March 20, 2018)

Sponsor/Partner	Disease Area/Antigen	GLA-SE Dose	# Receiving GLA-SE	# Total in Study
Oswaldo Cruz Foundation / IDRI NCT01154049	Schistosomiasis (Sm14)	10 mcg	20	20
IDRI / Rockefeller University NCT01397604 and NCT01864876	Adjuvant only	2 mcg 5 mcg	10 7	49
IDRI NCT01484548	Leishmaniasis (LEISH-F3)	2 mcg 5 mcg	12 12	36
NIAID / IDRI NCT01751048	Leishmaniasis (LEISH-F3)	5 mcg	16	48
IDRI NCT02071758	Leishmaniasis (LEISH-F3)	10 mcg	18	39
WRAIR / IDRI NCT01540474	Malaria (CelTOS)	2 mcg 5 mcg	10 20	30
European Vaccine Initiative / IDRI NCT01949909	Malaria (p27A)	2.5 mcg 5 mcg	24 8	56
European Vaccine Initiative / IDRI NCT02014727	Malaria (AMA-1 DiCo)	2.5 mcg	33	66
IDRI / Aeras NCT01599897	TB (ID93)	2 mcg 5 mcg	24 24	60
IDRI / Aeras NCT01927159	TB (ID93)	2 mcg 5 mcg	39 15	66
IDRI NCT02465216	TB (ID93)	2 mcg 5 mcg	20 28	60
CONFIDENTIAL	Seasonal influenza	0.5 mcg 1 mcg 2.5 mcg 5 mcg	6 12 36 4	96
Protein Sciences / Immune Design NCT01147068	Pandemic influenza (recombinant protein)	1 mcg	220	392
Novavax / Immune Design NCT01596725	Pandemic influenza (H5-VLP)	2.5 mcg	169	333
Medicago / Immune Design NCT01991561	Pandemic influenza (H5-VLP)	5 mcg	130	390
Immune Design NCT02015416	Cancer (NY-ESO-1)	2 mcg 5 mcg 10 mcg	3 3 6	12

Medimmune / Immune Design NCT02115815	Respiratory syncytial virus (sF)	2.5 mcg	60	144
Medimmune / Immune Design NCT02289820	Respiratory syncytial virus (sF)	1 mcg 2.5 mcg 5 mcg	39 99 79	261
Medimmune / Immune Design NCT02508194	Respiratory syncytial virus (sF)	5 mcg	946	1894

Table 4-6 Ongoing clinical trials using IDRI GLA-SE adjuvant formulations in combination with other vaccines (as of March 20, 2018)

Sponsor/Partner	Disease Area/Antigen	GLA-SE Dose	# Receiving GLA-SE	# Total in Study
IDRI NCT03302897	Leprosy (LEP-F1)	5 mcg	24	24
NIH/NIAID/DMID NCT02508376	TB (ID93)	5 mcg	20	70
University Hospital Tuebingen NCT02647489	Malaria (PAMVAC)	5 mcg	21	63
Institut National de la Santé Et de la Recherche Médicale NCT02658253	Malaria (PRIMVAC)	2.5 mcg	29	68
Immune Design NCT02035657	Merkel cell carcinoma	5 mcg	9	9
Immune Design NCT02501473	Non-Hodgkins lymphoma	5 mcg 10 mcg 20 mcg	3 3 4	10
Immune Design NCT02180698	Sarcoma	5 mcg 10 mcg 20 mcg	4 4 4	12
Immune Design NCT02387125	Cancer (CMB305, G305)	Not Available		
Immune Design NCT02609984	Cancer (CMB305)	Not Available		
Immune Design NCT02320305	Melanoma (MART1)	Not Available		
HVTN 115	HIV Vaccine	10 mcg	116	132

4.10 Potential risks of study products and administration

Table 4-7 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, decreased appetite, 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 and compare the safety and tolerability of the CH505TF gp120 proteins produced by transient and stable transfection in HIV-1–uninfected, healthy adults

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, and AEs and SAEs

Primary objective 2:

To evaluate and compare the magnitude of binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Primary endpoint 2:

HIV-specific total IgG binding antibody responses against the homologous proteins, as assessed by BAMA at peak timepoint (2 weeks after 3rd vaccination)

5.2 Secondary objectives and endpoints

Secondary objective 1:

To evaluate and compare the breadth and kinetics of binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Secondary endpoint 1:

HIV-specific total IgG binding antibody responses against the homologous proteins and magnitude-breadth (M-B) measures against panels of cross-clade Env proteins and of cross-clade V2 proteins, as assessed by BAMA at peak timepoints (2 weeks after the 2nd and 3rd vaccinations) and late timepoints (3 and 6 months after the 3rd vaccination)

Secondary objective 2:

To evaluate and compare the IgG subclass and IgA binding antibody responses elicited by the CH505TF gp120 proteins produced via transient and stable transfection methods

Secondary endpoint 2:

HIV-specific IgG subclass and IgA binding antibody response rates and magnitudes against homologous Env and V2 proteins, as assessed by BAMA at 2 weeks after the 2nd vaccination, 2 weeks after the 3rd vaccinations, and 3 and 6 months after the 3rd vaccination

Secondary objective 3:

To evaluate the ability of the two CH505TF gp120 proteins to elicit HIV-specific neutralizing antibodies (nAbs)

Secondary endpoint 3:

Magnitude and breadth of nAb responses against a panel of viral isolates as assessed by area under the M-B curves 2 weeks after the 2nd and 3rd vaccinations

Secondary objective 4:

To evaluate the avidity of antibody responses elicited by the CH505TF gp120 proteins

Secondary endpoint 4

Avidity of Env-specific IgG antibodies at baseline and 2 weeks after the 3rd vaccination

Secondary objective 5:

To evaluate HIV-specific T-cell responses induced by the two CH505TF gp120 proteins

Secondary endpoint 5:

Response rate, magnitude, and polyfunctionality of CD4+ T-cell responses as assessed by intracellular cytokine staining (ICS) assays 2 weeks after the 2nd and 3rd vaccinations

5.3 Exploratory objectives

Exploratory objective 1:

To evaluate the ability of the two CH505TF gp120 proteins to elicit memory B cells that differentially bind wildtype CH505 gp120Env vs mutant CH505 Env IΔ371 gp120

Exploratory objective 3:

To characterize the BCR repertoire of HIV-specific B cells

Exploratory objective 4:

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

Exploratory objective 5:

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 30 healthy, HIV-uninfected adult participants aged 18 to 50 years.

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 (Table 6-1) 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), there is a 90% chance of observing at least 1 event if the true rate of such an event is 15% or more; and there is a 90% chance of observing no events if the true rate is 0.5% or less. As a reference, in HVTN vaccine trials from December 2000 through April 2014, about 4% of participants who received placebos experienced an SAE.

Probabilities of observing 0, 1 or more, and 2 or more events among arms of size 15 are presented in Table 6-1 for a range of possible true AE rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with the vaccine.

Table 6-1 Probability of observing 0 events, 1 or more events, and 2 or more events, among arms of size 15, for different true event rates

True event rate (%)	Pr(0/15)	Pr(1+/15)	Pr(2+/15)
0.5	0.928	0.072	0.003
1	0.860	0.140	0.010
4	0.542	0.458	0.119
10	0.206	0.794	0.451
15	0.087	0.913	0.681
20	0.035	0.965	0.833
30	0.005	0.995	0.965
40	0.000	1.000	0.995

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 (50). If none of the 30 participants receiving a vaccine regimen experience a safety event, the 95% 2-sided upper confidence bound for the true rate of such events in the total vaccinated population (n = 30) is 11.4%. For each individual vaccine arm (n = 15), the 2-sided upper confidence bound for this rate is 20.4%.

Table 6-2 Two-sided 95% CIs based on observing a particular rate of safety endpoints for sample sizes 15 and 30

Observed event rate	95% CI (%)
0/15	[0.0, 20.4]
1/15	[0.3, 29.8]
2/15	[3.7, 37.9]
0/30	[0.0, 11.4]
1/30	[0.2, 16.7]
2/30	[1.8, 21.3]

6.1.2 Sample size calculations for immunogenicity

Binding antibodies will be measured by geometric mean fluorescence intensity (FI) for homologous proteins. We will test the null hypothesis that the geometric mean FI in the transient arm is less than 1/4 of the geometric mean FI in the stable arm. The power to reject this null hypothesis depends on the variability of the binding antibodies measurements and sample sizes. Based on HVTN 505 data, the standard deviation of the natural log of geometric mean FI at the dilutions optimized for immune correlates analyses, which maximize the proportion of samples within the linear range of the dilution-response curve, is around 1.4. Table 6-3 lists the power under a range of standard deviations, non-inferiority margins, and sample sizes.

The power study assumes that $\log_e$(geometric mean FI for a panel of Envs) is normally distributed and has the same spread in both arms. We will form a 95% confidence interval for the difference in $\log_e$(FI)s between the transient arm and the stable arm and compare the lower confidence interval to $\log_e(1/4)$. Under the parameters of the proposed study, the estimated power to reject the null hypothesis ranges from 0.86 to 0.63 for standard deviation ranging from 1.2 to 1.6.

Table 6-3 Power to reject the null hypothesis that the geometric mean FI in the transient arm is less than non-inferiority margin of the geometric mean FI in the stable arm. Standard deviation: spread of $\log_e$ (FI); n: sample size for each arm. The alpha level is set at 0.05 for a two-sided test.

Standard Deviation	Non-inferiority Margin								
	1/8	1/4	1/2	1/8	1/4	1/2	1/8	1/4	1/2
	$n = 10$			$n = 15$			$n = 20$		
1.2	0.96	0.69	0.23	1.00	0.86	0.33	1.00	0.95	0.43
1.4	0.88	0.55	0.18	0.98	0.74	0.26	1.00	0.86	0.33
1.6	0.78	0.45	0.15	0.93	0.63	0.21	0.98	0.76	0.27

6.2 Randomization

A participant's randomization assignment will be computer-generated and provided to the HVTN CRS pharmacist through a Web-based randomization system. 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 MOP).

6.3 Blinding

Participants and site staff (except for site pharmacists) will be blinded as to participant treatment arm assignments. Study product assignments are accessible to those 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.

In some cases, the CRS, PSRT, or study sponsor may believe unblinding of the site PI and participant would be appropriate to facilitate the clinical management of an AE or SAE. The HVTN Unblinding MOP specifies procedures for emergency unblinding, and for early unblinding for medical reasons.

6.4 Statistical analyses

This section describes the final study analyses, unblinded as to treatment arm assignment. All safety 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. The primary and secondary analyses of immunogenicity data are per-protocol in that only individuals who receive the expected vaccinations within the expected visit window contribute data.

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.

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. Wilcoxon 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 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 analyses will be 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 and difference between treatment arms will be presented with their corresponding 95% CI estimates calculated using the score test method (50).

For quantitative assay data, 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.

Mean or median (if normality assumption severely violated) assay readouts will be compared between arms and bootstrap CIs will be estimated.

More sophisticated analyses employing repeated measures methodology (for example, linear mixed models or marginal mean models fit by generalized estimating equations) may be utilized to incorporate immune responses over several timepoints and to test for differences over time.

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 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 heatmap showing the degree of correlation between any two 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 (51). 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 two 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 two arrows conveys information about the correlation of the two readouts, with a zero 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 Analysis of multiplexed immunoassay data

Two approaches will be considered to evaluate the magnitude and breadth of these responses. First, M-B curves maybe employed to display individual- and group-level response breadth as a function of magnitude. Two choices are to compare the M-B curves among vaccine arms, as follows: a non-parametric Wilcoxon rank sum test on the subject-specific area-under-the M-B curve (AUC-MB) or a Kolmogorov-Smirnov type test on the 2 group-average M-B curves. Simulations can be used to obtain 2-sided p-values for the latter test. Second, a weighted-average score-like variable may be constructed to account for the correlations between analytes as an integrate magnitude of responses to multiple analytes. Similar group comparison methods described in the first approach may be adopted. Details of either approach will be described in the SAP.

6.4.4.4 Analysis of neutralization magnitude-breadth curves

The area-under-the-magnitude-breadth curve (AUC-MB) to the panel of isolates will be computed for each participant with evaluable neutralization data, as described in Huang et al. (52). Methods for comparing AUC-MB are similar to those described in Section 6.4.4.3.

6.4.4.5 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 (53) 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 COMPASS (Combinatorial Polyfunctionality analysis of Antigen-Specific T-cell Subsets) statistical framework (54) 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 and data sharing 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 in accordance with Section 6.4.5.1. Interim blinded safety and immunogenicity data should not be shared outside of the SMB, HVTN 123 PSRT, the protocol team leadership, the HVTN Executive Management Team, the study product developer, and the study sponsor and/or its designee(s) for their regulatory reporting unless approved by the protocol leadership and the HVTN leadership.

6.4.5.1 Safety analyses

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 123 PSRT. Refer to the process described in the HVTN Unblinding MOP for any requests for unblinded safety data 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; completes a questionnaire prior to first vaccination with verbal demonstration of understanding of all questionnaire items answered incorrectly

5. **Willing to be contacted in person or by phone**, text message, or e-mail 6 months after completion of the scheduled clinic visits

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

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

HIV-Related Criteria

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

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

10. Assessed by the clinic staff as being at **"low risk" for HIV infection** and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit. (see Appendix I).

Laboratory Inclusion Values

Hemogram/Complete blood count (CBC)

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

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

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

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

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

Chemistry

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

Virology

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

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

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

Urine

20. **Normal urine**:

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

Reproductive Status

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

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

- Agree to use effective contraception for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment until 3 months after the final study vaccination. 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 123 PSRT
  - Successful vasectomy in any partner assigned male sex at birth (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy);
- Or not be of reproductive potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation;
- Or be sexually abstinent.

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

7.2 Exclusion criteria

General

1. **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 123 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 123 PSRT will determine eligibility on a case-by-case basis.

8. **Previous receipt of monoclonal antibodies (mAbs)**, whether licensed or investigational; the HVTN 123 PSRT will determine eligibility on a case-by-case basis.

9. **Non-HIV experimental vaccine(s) received within the last 5 years** in a prior vaccine trial. Exceptions may be made by the HVTN 123 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 123 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 123 PSRT on a case-by-case basis.

10. **Live attenuated vaccines** received within 30 days before first vaccination or scheduled within 14 days after injection (eg, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever)

11. **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)

12. **Allergy treatment with antigen injections** within 30 days before first vaccination or that are scheduled within 14 days after first vaccination

Immune System

13. **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 oral/parenteral prednisone or equivalent at doses $\leq$ 60 mg/day and length of therapy < 11 days with completion at least 30 days prior to enrollment)

14. **Serious adverse reactions to vaccines** 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.)

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

16. **Autoimmune disease**

17. **Immunodeficiency**

Clinically significant medical conditions

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 exclusion criteria:**

    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 (Not excluded: type 2 cases controlled with diet alone or a 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 three years. Also exclude if volunteer has used medications in order to prevent or treat seizure(s) at any time within the past 3 years.

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 study product administration schedule. Pause rules for the trial are described in Section 11.3.

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
  - Receipt of allergy treatment with antigen injections
- Within 14 days prior to any study injection
  - Receipt of any vaccines that are not live attenuated vaccines (eg, pneumococcal)
- Prevaccination 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 123 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 123 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)
  - HIV infection
  - 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 that is subsequently considered to be related to vaccination
  - Other grade 3 clinical AE that is subsequently considered to be related to vaccination with the exception of fever, vomiting, and subjective local and systemic symptoms. For grade 3 injection site erythema and/or induration, upon review, the PSRT may allow continuation of vaccination

  - SAE that is subsequently considered to be related to vaccination
  - Clinically significant type 1 hypersensitivity reaction associated with study vaccination. Consultation with the HVTN 123 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)

Participants discontinuing study product for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated (See HVTN 123 SSP).

Participants diagnosed with HIV infection during the study should be encouraged to participate in follow-up visits as indicated in Section 9.13

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, or
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff).
- Any condition where termination from the study is required by applicable regulations.

8 Study product preparation and administration

The 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 IBs 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): 100 mcg of Stable CH505TF gp120 admixed with 10 mcg of GLA-SE, to be administered as a 1mL IM injection in the deltoid of the non-dominant arm at Months 0, 2, and 6.

Group 2

Treatment 2 (T2): 100 mcg of Transient CH505TF gp120 admixed with 10 mcg of GLA-SE, to be administered as a 1mL IM injection in the deltoid of the non-dominant arm at Months 0, 2, and 6.

8.2 Study product formulation

8.2.1 Stable CH505TF gp120

The Stable CH505TF gp120 will be provided at a concentration of 0.8 mg/mL of protein in phosphate-buffered saline per vial. Each sterile, single use vial contains 0.75 mL of study product. The study product must be stored frozen at ≤ -65°C. When thawed, the Stable CH505TF gp120 will be clear, and colorless to slightly yellow, liquid. The study product is described in further detail in the IB.

8.2.2 Transient CH505TF gp120

The Transient CH505TF gp120 will be provided at a concentration of 0.8 mg/mL of protein in phosphate-buffered saline per a vial. Each sterile, single use vial contains 0.7 mL of study product. The study product must be stored frozen at ≤ -65°C. When thawed, the Transient CH505TF gp120 will be clear, and colorless to slightly yellow, liquid. The study product is described in further detail in the IB.

8.2.3 GLA-SE (Glucopyranosyl Lipid Adjuvant-Stable Emulsion)

The GLA-SE adjuvant will be provided at a concentration of 20 mcg/mL GLA in a 4% oil-in-water emulsion in a vial. Each sterile, single use vial contains 0.4 mL of this mixture, which appears as a milky-white liquid. GLA-SE must be stored at 2-8°C and must not be frozen. The study product is described in further detail in the IB.

8.3 Preparation of study products

8.3.1 Group 1 (T1): 100 mcg of Stable CH505TF gp120 + 10mcg of GLA-SE

One vial of Stable CH505TF gp120 (0.8 mg/mL) and two vials of GLA-SE (20 mcg/mL) will be needed to prepare the dose.

Prior to admixture, the pharmacist will remove a vial of Stable CH505TF gp120 from the freezer and allow to thaw completely at room temperature. Once thawed completely, invert the vial 10 times to ensure a homogeneous product. Remove two vials of GLA-SE from the refrigerator and allow to equilibrate to room temperature.

Using aseptic technique, the pharmacist will add 0.5 mL of Stable CH505TF gp120 and 1.5 mL of Sodium Chloride for injection, 0.9% USP to an empty sterile vial. Mix the contents of this vial thoroughly using a vortex machine at high speed for 3 seconds. The final concentration of Stable CH505TF gp120 is 200 mcg/mL.

Next, using aseptic technique, withdraw 0.6 mL of the diluted 200 mcg/mL Stable CH505TF gp120 admixture and 0.6 mL of GLA-SE (20 mcg/mL) and inject it into an empty sterile vial. Mix thoroughly by gently inverting 10 times, yielding a concentration of 100 mcg/mL Stable CH505TF gp120 and 10 mcg/mL GLA-SE.

Finally, using aseptic technique, withdraw 1 mL from the vial containing 100 mcg/mL Stable CH505TF gp120 and 10 mcg/mL GLA-SE, using a 3 or 5 mL size syringe. Remove the needle and cap syringe.

The prepared syringe for administration must be covered with an overlay and then labeled as “Stable CH505TF/GLA-SE or Transient CH505TF/GLA-SE”. The syringe must also be labeled for IM administration into the deltoid of the non-dominant arm, with an expiration date and time of 8 hours following the last mixing procedure.

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

8.3.2 Group 2 (T2): 100 mcg of Transient CH505TF gp120 + 10 mcg of GLA-SE

One vial of Transient CH505TF gp120 (0.8 mg/mL) and two vials of GLA-SE (20 mcg/mL) will be needed to prepare the dose.

Prior to admixture, the pharmacist will remove a vial of Transient CH505TF gp120 from the freezer and allow to thaw completely at room temperature. Once thawed completely, invert the vial 10 times to ensure a homogeneous product. Remove two vials of GLA-SE from the refrigerator and allow to equilibrate to room temperature.

Using aseptic technique, the pharmacist will add 0.5 mL of Transient CH505TF gp120 and 1.5 mL of Sodium Chloride for injection, 0.9% USP to an empty sterile vial. Mix the contents of this vial thoroughly using a vortex machine at high speed for 3 seconds. The final concentration of Transient CH505TF gp120 is 200 mcg/mL.

Next, using aseptic technique, withdraw 0.6 mL of the diluted 200 mcg/mL Transient CH505TF gp120 admixture and 0.6 mL of GLA-SE (20 mcg/mL) and inject it into an empty sterile vial. Mix thoroughly by gently inverting 10 times, yielding a concentration of 100 mcg/mL Transient CH505TF gp120 and 10 mcg/mL GLA-SE.

Finally, using aseptic technique, withdraw 1 mL from the vial containing 100 mcg/mL Transient CH505TF gp120 and 10 mcg/mL GLA-SE, using a 3 or 5 mL size syringe. Remove the needle and cap syringe.

The prepared syringe for administration must be covered with an overlay and then labeled as “Stable CH505TF/GLA-SE or Transient CH505TF/GLA-SE”. The syringe must also be labeled for IM administration into the deltoid of the non-dominant arm, with an expiration date and time of 8 hours following the last mixing procedure.

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

8.4 Administration

All injections should be administered in the deltoid of the non-dominant arm.

The prepared study product in the syringe should be rolled gently prior to administration.

The prepared study product in the syringe must be administered as soon as possible and before the 8-hour expiration.

Any administrator of study product will be blinded to the individual participant's treatment assignment.

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.

Group 1 (T1):

100 mcg of Stable CH505TF gp120 admixed with 10 mcg of GLA-SE, to be administered as a 1mL IM injection in the deltoid of the non-dominant arm at Months 0, 2, and 6.

Group 2 (T2):

100 mcg of Transient CH505TF gp120 admixed with 10 mcg of GLA-SE, to be administered as a 1mL IM injection in the deltoid of the non-dominant arm at Months 0, 2, and 6.

8.5 Acquisition of study products

Stable CH505TF gp120, Transient CH505TF gp120, and GLA-SE will be provided by DAIDS. Sodium Chloride for injection, 0.9% USP 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 outlined 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

For US clinical research sites, all unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by

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

9 Clinical procedures

The schedule of clinical procedures is shown in Appendix F .

9.1 Informed consent

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

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

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

Note: As defined in the DAIDS Protocol Registration Manual, an RE is "Any group other than the local IRB/EC responsible for reviewing and/or approving a clinical research protocol and site-specific 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 ICH E6, Good Clinical Practice: Consolidated Guidance 4.8.

Study sites are strongly encouraged to have their local CABs review their sites-specific consent forms. This review should include, but should not be limited to, issues of cultural competence, local language considerations, and the level of understandability.

The sample informed consent forms include instructions throughout the document for developing specific content.

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

9.1.3 Assessment of Understanding

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

An Assessment of Understanding is used to document the participant's understanding of key concepts in this 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 including:
  - Screening HIV test,
  - HBsAg,
  - Anti-HCV antibodies,
  - CBC with differential and platelets,
  - Chemistry panel (ALT, AST, alkaline phosphatase, and creatinine),
  - Urine dipstick (as described in Section 9.8), and
  - Urine or serum pregnancy test (participants who were assigned female sex at birth)

- Syphilis test
- 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)
- Behavioral risk assessment
- 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 9.6
- Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in study inclusion criteria. Discussion of pregnancy prevention includes advising a participant who was assigned female sex at birth and who reports no current sexual activity that could lead to that participant becoming pregnant to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

9.2.1 Use of screening results from another HVTN study

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

9.3 Enrollment 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 assigned female sex at birth). 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 Participant Diary 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 9.9).

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 9.6);
- Pregnancy prevention assessment (as described in Section 9.2 and 9.7); 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 E and Appendix F:

- HIV infection assessment including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- 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;

- 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);
- Behavioral risk assessment; and
- Specimen collection (must be performed 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 9.6);
- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation);
- Assessment of new or continuing concomitant medications (as described in Section 9.2);
- Assessment of new or unresolved AEs/intercurrent illnesses; and
- Specimen collection.

Additional procedures will be performed at scheduled follow-up visits as specified in Appendix E and 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;
- Pregnancy prevention assessment (as described in Section 9.2 and 9.7);
- Behavioral risk assessment;
- HIV infection assessment including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;

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

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

- Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;

- Clinical laboratory tests including:
  - CBC with differential and platelets,
  - Chemistry panel (see Section 9.2), and
  - Urine dipstick (urinalysis if appropriate; see Section 9.8); and

- Urine or serum pregnancy test (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

9.5 AESI health contact

CRS staff will contact study participants 18 months after enrollment to collect the information listed below. Clinic visits will only be required if HIV confirmatory testing is necessary (see Section 9.6.1); however, a clinic visit may be arranged for other reasons.

- Confirmation of vital status; if deceased, attempt to learn cause and date of death;

- If participant is alive, record the following events:
  - New AEs related to study product(s)
  - AEs of special interest (AESI, see Section 11.2.2). A sample list of AESI is provided in Appendix H. AESI are reported regardless of relationship to study product(s);
  - New diagnosis of HIV infection; and
  - Pregnancies and outcomes, including congenital anomalies/birth defects.

All such events will be recorded, and AEs will be assessed for relationship to study product(s).

9.5.1 Interim contacts

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

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

9.6.1 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.

9.6.2 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 9.6.1). 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.

9.7 Contraception status

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

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.

9.8 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.

9.9 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 (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, except as noted in Section 11.2.2.

The reactogenicity assessment period is 7 full days following each vaccination per the assessment schedule shown in Table 9-1. Participants are instructed to record symptoms using a Participant Diary. Contacts between the participant and the site

staff should take place at least once between 1-3 days postvaccination. 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. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 7 to resolution.

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, and vaccine-related lesions. 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/AEs requiring expedited reporting to DAIDS criteria, are recorded on an adverse experience log form.

Table 9-1 Schedule of reactogenicity assessments

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

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

9.9.1 Assessment of systemic and local symptoms

Systemic symptoms include increased body temperature, malaise and/or fatigue, myalgia, headache, chills, arthralgia, and nausea. 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. All temperatures must be measured by non-axillary thermometry. This includes temperatures taken in the clinic, as well as temperatures taken by participants during the reactogenicity period.

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

9.9.2 Assessment of injection site

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

All injection site reactions are monitored until resolution. Reactions with diameters greater than 5 cm are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

9.10 Visit windows and missed visits

Visit windows are defined in HVTN 123 SSP. For a visit not performed within the window period, a Missed Visit form is completed. If the missed visit is one that required safety assessments or local safety labs, 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.

9.11 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 platelets, and chemistry panel), pregnancy testing, social impact assessment, and HIV test. For participants who have a confirmed diagnosis of HIV infection, see Section 9.13

9.12 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.

9.13 HIV infection during the study

If a participant becomes HIV-infected during the course of the study, no additional study product will be administered. Participants will be encouraged to continue scheduled study visits for up to 6 months following their last study product administration. Follow-up duration for participants diagnosed with HIV infection may be adjusted in consultation with the CRS investigator and the HVTN 123 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At post-infection follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis and pregnancy tests will be

collected; in addition, some clinic procedures may be modified or discontinued (see Appendix E and Appendix F).

10 Laboratory

10.1 HVTN CRS laboratory procedures

The HVTN 123 Site Lab Instructions and SSP provide further guidelines for operational issues concerning the clinical and processing laboratories. These documents include guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

Tube types for blood collection are specified in Appendix 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.

Of note, all assays described below are performed as research assays to evaluate the ability of the vaccine to induce immune responses in the context of the participants' genetic background, and are not approved for use in medical care. Results from these assays are not made available to participants or medical professionals to guide treatment decisions.

10.2 Total blood volume

Required blood volumes per visit are shown in Appendix 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 Immunogenicity timepoints

The immunogenicity timepoints in this study occur: 2 weeks after the 2nd vaccination visit, 2 weeks after the 3rd vaccination visit, 3 months after the 3rd vaccination visit, and 6 months after the 3rd vaccination visit. Endpoint assays for humoral and cellular responses are performed on samples collected from participants at the immunogenicity timepoints and may be performed on samples collected at baseline. Depending on the initial results, assays for humoral and cellular responses may be performed on samples collected from participants at other timepoints; the schedule is shown in Appendix E.

10.4 Endpoint assays: cellular

10.4.1 Flow cytometry: ICS

Flow cytometry will be used to examine vaccine-specific CD4+ T-cell responses following stimulation of peripheral blood mononuclear cells (PBMCs) with synthetic HIV peptides that span the proteins encoded by the vaccine. ICS parameters will include cytokines such as interferon (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. Data will be reported as percentages of CD4+ T cells responding to a specific peptide pool. Additional cell surface markers, cytokines, or functional markers may also be analyzed.

10.4.2 Flow cytometry: antigen-specific B cell phenotyping assay

Antigen-specific B cells induced by vaccination will be identified and characterized using fluorescently-labeled recombinant proteins in combination with a flow cytometry phenotyping panel. In particular, HIV Env-reactive B cells will be enumerated and may be further characterized for expression of memory, activation, inhibitory or other markers of interest. B cells may also be sorted for further analysis by BCR sequencing or gene expression analysis. B cells may instead be cultured for detection of and functional testing of secreted antibodies by ELISA or microneutralization assays, and/or BCR sequencing.

10.4.3 BCR repertoire analysis

Single or bulk populations of naïve or memory B cells, or plasmablasts, may be sorted for any combination of BCR sequencing, gene expression analysis, or functional antibody testing by microneutralization or binding assays.

10.5 Endpoint assays: humoral

10.5.1 Binding antibody multiplex assay (BAMA)

HIV-1–specific total binding IgG antibodies to CH505TF gp120 and a panel of heterologous gp120s will be assessed on serum samples from study participants taken at the primary immunogenicity timepoints and baseline. In addition, HIV-1–specific total binding IgA antibodies and binding to IgG subclasses (IgG1, IgG2, IgG3, and IgG4) may also be assessed. Specimens from other timepoints may also be assayed based on the results of the initial assay.

10.5.2 Neutralizing antibody (nAb) 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 strains (CH505TF, CH505.w4.3) and a single highly neutralization-sensitive Tier 1 virus as a positive control. The global panel and/or clade-specific panels may be used to assess Tier 2 neutralization (55, 56).

10.5.3 Antibody avidity

Antibody avidity will be measured using BAMA with the addition of a dissociation step to calculate the avidity index or by surface plasmon resonance assay.

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 genes, including those associated with immune responses (eg, immunoglobulin or T-cell receptor genes) or HIV-1 disease 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.

10.9 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 (see Appendix A).

This research may relate to HIV, vaccines, the immune system, and other diseases. This could include genetic testing and, potentially, genome-wide studies. This research is done only to the extent authorized in each study site's informed consent form, or as otherwise authorized under applicable law. Other research on specimens ("other use") will occur only after review and approval by the HVTN, the 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 123 PSRT

The HVTN 123 PSRT is composed of the following members:

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

The clinician members of HVTN 123 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 123 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 during the main study, as defined in Section 3. 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 123 PSRT.

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

11.1.3 SDMC roles and responsibilities in safety monitoring

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

- Maintaining a central database management system for HVTN clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 123 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 123 PSRT AE review criteria (see Section 11.3);
- Notifying HVTN CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.3);
- Querying HVTN CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 123 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

Site staff must submit all safety forms (eg, reactogenicity, adverse experience, urinalysis, local lab results, and concomitant medications) before the end of the next business day, excluding federal or bank holidays. The forms should not be held in anticipation of additional information at a later date. If additional information is received at a later date, the forms should be updated and resubmitted before the end of the next business day after receiving the new information. For the case of a longer site holiday closure, site staff must submit the data by the end of the 5th day (local time) after receiving the information even if this day is a holiday.

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

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). All AEs are graded according to the Division of AIDS

(DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables, except:

- Unintentional Weight Loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 123 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 main study period (see Section 3) all AEs are reported to the SDMC on the appropriate CRF. Clinic staff should evaluate every AE to determine if (1) the AE meets the requirements for expedited reporting to DAIDS (see Section 11.2.3) and (2) if the AE meets the criteria for a prompt AE review (see Section 11.3).

After the main study period, report the subset of AEs bulleted in Section 9.5 until the AESI health contact (see Section 3) is complete.

Sites are expected to notify HVTN clinical safety staff of any serious safety concern requiring their attention (Table 11-1). Telephone numbers and email addresses are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn123). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

In the case of email notification, clinical safety staff will reply during working hours (local time) to confirm that the email has been received and reviewed. If email service is not available, the CRS should notify clinical safety staff of the event by telephone, then submit CRFs.

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

11.2.3 Expedited reporting of adverse events to DAIDS

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

The internet-based DAIDS Adverse Experience Reporting System (DAERS) must be used for expedited AE (EAE) reporting to DAIDS. In the event of system outages or technical difficulties, EAE reports may be submitted via the DAIDS EAE Form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact CRMSsupport@niaid.nih.gov or from within the DAERS application itself.

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

The study products for which expedited reporting are required are:

- Stable CH505TF HIV gp120 with GLA-SE
- Transient CH505TF HIV gp120 with GLA-SE

While the participant is in the main study reporting period (see Section 3), the SAE Reporting Category will be used.

After completion of the main study period through completion of the AESI health contact (see Section 3) the SUSAR Reporting Category will be used.

After the participant has completed the AESI health contact and is off study, sites must report SUSARS if the study site staff becomes aware of the events on a passive basis (eg, from publicly available information).

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 study sponsor Medical Officer will not routinely be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

In some cases, the PSRT or CRS may believe unblinding of the site PI and participant would be appropriate to facilitate the clinical management of an AE or

SAE. The HVTN MOP specifies procedures for emergency unblinding, and for early unblinding for medical reasons.

11.3 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 123 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 123 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 PSRT notification
SAE, related	Grade 3, 2, or 1	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause
AE[b], related	Grade 4 or 3	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause

[a] Phone numbers and email addresses are found on the Protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn123).

[b] Does not include the following Grade 3 subjective reactogenicity symptoms:injection site pain, tenderness, fatigue/malaise, myalgia, arthralgia, chills, headache, nausea (unless IV rehydration required).

For all safety pauses, HVTN Core notifies the HVTN 123 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 123 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 123 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 123 PSRT notification or prompt HVTN 123 PSRT AE review is triggered, HVTN Core notifies the HVTN 123 PSRT as soon as possible during working hours (local time)—or, if the information was received during off hours, by the morning of the next workday. If a prompt HVTN 123 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, unanticipated problems involving risks to participants or others, and notification of other unplanned safety pauses). CRSs must also follow all applicable RE reporting requirements.

In addition, all other AEs are reviewed routinely by the HVTN 123 PSRT (see Section 11.4.2).

11.4 Review of cumulative safety data

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

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

11.4.1 Daily review

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 123 PSRT AE review criteria.

11.4.2 Weekly review

During the injection phase of the trial, the HVTN 123 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 123 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the HVTN CRS clinic coordinator for verification.

11.5 Study termination

This study may be terminated early by the determination of the HVTN 123 PSRT, a pertinent national regulatory authority, NIH, Office for Human Research

Protections (OHRP), FDA, or study product developer(s). In addition, the conduct of this study at an individual HVTN CRS may be terminated by the determination of the IRB/EC and any applicable RE.

12 Protocol conduct

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

- Protocol registration, activation, and implementation;
- Informed consent, screening, and enrollment;
- Study participant reimbursement;
- Clinical and safety assessments;
- Safety monitoring and reporting;
- Data collection, documentation, transfer, and storage;
- Participant confidentiality;
- Study follow-up and close-out;
- 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;
- Exploratory and ancillary studies and sub-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 123 *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 can contact the participant without IRB/EC approval if such communication is necessary to avoid imminent harm to the study participant. The CRS must notify the IRB/EC and any applicable RE of the matter as soon as possible.

13 Version history

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

The version history of, and modifications to, Protocol HVTN 123 are described below.

Protocol history and modifications

Date: December 12, 2018

Protocol version: 1.0
Protocol modification:

Original Protocol

14 Document references (other than literature citations)

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

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines.
  - Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf
  - Revised Guidelines for HIV Counseling, Testing, and Referral. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm
- Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
- Division of AIDS Protocol Registration Manual. Available at https://www.niaid.nih.gov/sites/default/files/prmanual.pdf
- Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, July 2017. Available at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 123 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 123 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN 123 Site Lab Instructions. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.

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

- Lab assay algorithm (available upon request)

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

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

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

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

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

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

- Title 45, Code of Federal Regulations, Part 46. Available at https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html

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

15 Acronyms and abbreviations

aa	amino acid
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUC	area under the curve
AUC-MB	area under the magnitude-breadth curve
AVEG	AIDS Vaccine Evaluation Group
BAMA	binding antibody multiplex assay
BCR	B-cell receptor
BDS	bulk drug substance
β-HCG	beta human chorionic gonadotropin
BMI	body mass index
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CD4-BS	CD4 binding site
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CI	confidence interval
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
DHVI	Duke Human Vaccine Institute
DSC	differential scanning calorimetry
DSMB	NIAID Data and Safety Monitoring Board
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
Envs	envelope proteins
FDA	US Food and Drug Administration
FI	fluorescence intensity

Fred Hutch	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GLA-SE	glucopyranosyl lipid adjuvant-stable emulsion
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
IBC	Institutional Biosafety Committee
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICS	intracellular cytokine staining
IDRI	Infectious Disease Research Institute
IFN	interferon
IM	intramuscular
IND	Investigational New Drug
IL	interleukin
IRB	Institutional Review Board
ITC	Isothermal titration calorimetry
IUD	intrauterine device
LTFU	loss to follow-up
mAb	monoclonal antibody
M-B	magnitude-breadth
MMR	measles, mumps, and rubella
nAb	neutralizing antibody
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases (US NIH)
NIH	US National Institutes of Health
NZW	New Zealand White
OHRP	US Office for Human Research Protections
OPV	oral polio vaccine
PAB	DAIDS Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PCR	polymerase chain reaction
PI	Principal Investigator

PCA	principal component analysis
PSRT	Protocol Safety Review Team
RAB	DAIDS Regulatory Affairs Branch
RE	regulatory entity
RSC	DAIDS Regulatory Support Center
RSV	respiratory syncytial virus
SAE	serious adverse event
SAP	statistical analysis plan
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SEC	size exclusion chromatography
SMB	Safety Monitoring Board
SPT	DAIDS Safety and Pharmacovigilance Team
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Tm	melting temperature
TNF	tumor necrosis factor
UCA	unmutated common ancestor
UW-VSL	University of Washington Virology Specialty Laboratory
Ve	elution volume
VISP	Vaccine-induced seropositivity

16 Literature cited

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Appendix A Sample informed consent form

Title: A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1–uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

HVTN protocol number: HVTN 123

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 HIV vaccines. HIV is the virus that causes AIDS.

About 30 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.**

   - Are the study vaccines safe to give to people?
   - Are people able to take the study vaccines without becoming too uncomfortable?
   - How do people's immune systems respond to the study vaccines? (Your immune system protects you from disease.)
   - Does a small difference in the way the 2 vaccines were made change how people's immune systems respond?

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

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

3. **We do not know if the study vaccines 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. You can remove the box around the text.

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.

This study differs from the studies in which people who got the vaccine had a higher or lower risk of getting HIV. We can tell you about the differences.

We do not know whether the vaccines 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. **These study vaccines are experimental.**

The study vaccines are protein vaccines called Stable CH505TF gp120 and Transient CH505TF gp120. From here on, we will call them **gp120S and gp120T study vaccines**. They are experimental HIV vaccines. That means we do not know if the vaccines will be safe to use in people, or if they will work to prevent HIV infection. These vaccines are used only in research studies.

For both vaccines, first DNA is used in a lab to tell cells how to make the protein. The gp120S vaccine was made by having the DNA that makes the protein become a part of the DNA of the cell. For the gp120T vaccine, the DNA that makes the protein was put into the cells, but did not become a part of the cell's DNA. In both cases, after the protein is made, it is separated from the cells and purified into a vaccine.

The vaccines were developed by the Division of AIDS (DAIDS) at the National Institutes of Health (NIH). The vaccines have man-made pieces of protein that look like part of the protein found in HIV. Your body's immune system might learn to recognize these proteins and prepare itself to fight HIV. This is called an immune response.

The vaccines are mixed with an adjuvant. An adjuvant is a substance added to the vaccine to help the immune system respond better. The adjuvant in this study is called GLA-SE. GLA-SE was made by Infectious Disease Research Institute (Seattle, Washington, USA).

The gp120S and gp120T vaccines are very similar protein vaccines made in the laboratory in two slightly different ways.

The gp120S study vaccine has been tested in animals and it did not cause any health concerns. Animal testing may not always tell us what will happen with humans. It has been given to about 42 people in another study that is ongoing and has not caused serious health problems. If we learn anything from that study that might affect your participation in this study, we will tell you.

The gp120T study vaccine has not been given to people before. Similar vaccines to those being used in this study have been given to thousands of people and have not caused 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.

Risks of the study vaccines:

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

The gp120S vaccine with the GLA-SE adjuvant has been given to a small number of people in a study that is still going on. The most common complaints have been pain or tenderness where they got the injection. One person had a skin infection where they got the injection. It did not affect that person’s daily routine. That person took some medicine and it got better within 5 days.

The gp120T study vaccine has not been given to people before.

The adjuvant, GLA-SE, has also been tested in over 900 people with vaccines for other diseases. The most common complaints were pain and tenderness where they got the injection and feeling tired.

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

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

You should not become pregnant during the study because we do not know how the study vaccines could affect the developing baby. You must agree to use effective birth control from 21 days before your first injection until 3 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).

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

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 gp120S study vaccine or the gp120T study vaccine.

Half the people in this study will get the gp120S study vaccine and half will get the gp120T study vaccine. We will compare the results.

Whether you get the gp120S or gp120T study vaccine is completely random, like flipping a coin.

We have no say in whether you get the gp120S or gp120T study vaccine. 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 gp120S or gp120T study vaccine. 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 products on a schedule.

You will be in one of 2 groups. You will get 3 injections during the study in your upper arm.

Group	Injection Schedule		
	First injection	2 month later	6months later
1	gp120S	gp120S	gp120S
2	gp120T	gp120T	gp120T

You will have to wait in the clinic for about a half hour after each injection to see if there are any problems. Then for 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 each injection, we will also ask you how you are doing. Contact the clinic staff 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 products, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV
- Do physical exams

- Do pregnancy tests if you were assigned female sex at birth
- Ask questions about your health, including medications you may be taking
- Ask questions about any personal problems or benefits you may have from being in the study
- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 10 mL and 275 mL (2 teaspoons to a little over 1 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, which are located in the United States. In rare cases, some of your samples may be sent to labs approved by the HVTN in other countries for research related to this study.

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

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

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

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

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

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

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

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.

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 do research with them.

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it, but your name and other personal information will not be included. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small. There may be other unknown risks.

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

People who may see your information are:

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

- Any regulatory agency that reviews clinical trials,
- The researcher's IRB or EC
- 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. You can remove the box around the text.

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 (FDA),
- Any regulatory agency that reviews clinical trials,

- [Insert name of local IRB/EC] ,
- [Insert name of local and/or national regulatory authority as appropriate],
- Infectious Disease Research Institute (IDRI) 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 around the text.

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 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.

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

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

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

We will encourage you to stay in the study for up to 6 months if you choose. We will discuss your study options with you. We will counsel you about your HIV infection and about telling your partner(s). We will tell you where you can get support and medical care. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

Other Risks

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 HIV study vaccines. The study vaccines 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 vaccines, 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 vaccines.

If you have a positive test result caused by the study vaccines 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 vaccines. 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 vaccines, 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 six 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.

US sites, include the following paragraph In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

Unknown risks:

We do not know if the study vaccines 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(s)] might affect your HIV infection or how long it takes to develop AIDS.

We do not know if getting these study vaccines will affect how you respond to any future approved HIV vaccine. Currently, no HIV vaccine has been approved for use.

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

Benefits

22. The study may not benefit you.

We do not expect the study vaccines to 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 vaccines later become approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

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

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

Leaving the study

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

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

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

Injuries

Sites: 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. You can remove the box around the text.

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

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

If you become sick or injured in this study, there is a process to decide if it is related to the study products 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. *(Sites: insert locale- appropriate medical insurance language in the following sentence)* If the injury is not study related, then you and your health insurance will be responsible for treatment costs.

Some injuries are not physical. For example, you might be harmed emotionally by being in an HIV 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.

Health contact visit

26. After your clinic visits end, we will contact you 18 months after your first injection.

We will contact you by phone, email, or text message *[Site: Modify mode of contact as appropriate; consult IRB/EC if necessary]* 18 months after your first injection to ask questions about your health. If you prefer to answer these questions in person, you can come to the clinic to do this.

If we have any concerns about your health, we may need to have more contact with you. You are also welcome to contact us at any time if you have concerns about your health related to being in the study.

If we ask you to come to the clinic, we will give you
[Site: Insert compensation amount] for each visit. This amount is to cover the costs of [Site: Insert text].

If someone outside this study clinic told you that you are infected with HIV, we will ask you to come back to the clinic for another HIV test. We will draw about 15 mL (1 tablespoon) of blood. We may ask you to come back more than once for this testing.

Because we will want to contact you after the main study, please tell us if your contact information changes, if you are moving away, or if you do not want us to contact you anymore.

You can tell us at any time that you don't want us to contact you after the main study. If you do so, you will not lose any benefits or rights you would normally have.

All other information that is discussed earlier in this consent also applies to the 18 month health contact.

Questions

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

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

If you have any symptoms that you think may be related to this study, contact
[name or title and telephone number of the investigator or other study staff].

This study has been reviewed and approved by a committee called the
[name of local IRB/EC]. If you have questions about your rights as a research participant, or problems or concerns about how you are being treated in this study, contact
"[name or title and telephone number of person on IRB/EC]" , at the committee.

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

Your permissions and signature

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

28. In Section 15 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. You can change your mind after signing this form.

☐ I allow my extra samples and information to be used for other studies related to HIV, 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.

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

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

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

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

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

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

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

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

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

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

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

You must agree to use effective birth control from 21 days before your first injection until 3 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 partner(s) assigned female sex at birth;
- You only have oral sex; or,
- You are sexually abstinent (no sex at all).

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

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

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

Title: A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1–uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

HVTN protocol number: HVTN 123

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 HVTN or other researchers. Once we share your samples and information, we may not be able to get them back.

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

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

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

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

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

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

Researchers may also do genetic testing on your samples.

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

If you agree, your samples could also be used for genome wide studies. In these studies, researchers will look at all of your genes (your genome). The researchers compare the genomes of many people, looking for common patterns of genes that could help them understand diseases. The researchers may put the information from the genome-wide studies into a protected database so that other researchers can access it, but your name and other personal information will not be included. Usually, no one would be able to look at your genome and link it to you as a person. However, if another database exists that also has information on your genome and your name, someone might be able to compare the databases and identify you. If others found out, it could lead to discrimination or other problems. The risk of this is very small. There may be other unknown risks.

10. What are the risks of genetic testing?

It is unlikely, but the genetic tests done on your samples could show you may be at risk for certain diseases. If others found out, it could lead to discrimination or other problems. However, it is almost impossible for you or others to know your test results from the genetic testing. The results are not part of your study records and are not given to you.

US sites, include the following paragraph

In the very unlikely event that your genetic information becomes linked to your name, a federal law called the Genetic Information Nondiscrimination Act (GINA) helps protect you. GINA keeps health insurance companies and employers from seeing results of genetic testing when deciding about giving you health insurance or offering you work. GINA does not help or protect you against discrimination by companies that sell life, disability or long-term care insurance.

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

People who may see your information are:

- Researchers who use your extra samples and information for other research
- Government agencies that fund or monitor the research using your extra samples and information
- Any regulatory agency that reviews clinical trials,
- The researcher's IRB or EC
- The people who work with the researcher

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

Questions

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

If you have questions about the use of your samples or information or if you want to change your mind about their use, contact
[name or title and telephone number of the investigator or other study staff].

If you think you may have been harmed because of studies using your samples or information, contact
[name or title and telephone number of the investigator or other study staff].

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

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

☐ I allow my extra samples and information to be used for other studies related to HIV, 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 entire discussion of this consent form.

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

Procedure	Screening visit	First injection visit	Time after first injection visit							
			2 weeks	2 months	2 months + 2 weeks	6 months	6 months + 2 weeks	9 months	12 months	18 months[2]
Injection		√		√		√				
Medical history	√									
Complete physical	√								√	
Brief physical		√	√	√	√	√	√	√		
Urine test	√		√				√			
Blood drawn	√	√	√		√	√	√	√	√	
Pregnancy test (participants assigned female sex at birth)[1]	√	√		√		√		√		
HIV testing and pretest counseling	√				√	√		√	√	
Risk reduction counseling	√	√	√	√	√	√	√	√	√	
Interview/ questionnaire	√	√	√	√	√	√	√	√	√	
Health contact										√

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

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

[2]Visit at 18 months is a health contact visit.

Appendix E Laboratory procedures (1of 2)

					Tube volume (mL)									
				Visit:	**1**	**2**	**3**	4	**5**	**6**	**7**	**8**	**9**	
				Day:	Screening visit[3]	D0	D14	D56	D70	D168	D182	D273	D364	
				Week:		W0	W2	W8	W10	W24	W26	W39	W52	
				Month:		M0	M0.5	M2	M2.5	M6	M6.5	M9	M12	
						VAC1		**VAC2**		**VAC3**				
Procedure	**Ship to[1]**	**Assay Location[2]**	**Tube[4]**	**Tube size (vol. capacity)[4]**										**Total**
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[11]														
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	FHCRC	ACD	8.5mL	—	17	—	—	—	—	—	—	—	17
Cellular assays														
ICS	CSR	HVTN Labs	ACD	8.5mL	—	42.5	—	—	***59.5***	—	***59.5***	—	42.5	204
Ag-specific B cell phenotyping	CSR	HVTN Labs	ACD	8.5mL	—	42.5	—	—	***42.5***	—	***42.5***	—	42.5	170
B cell repertoire analysis	CSR	HVTN Labs	ACD	8.5mL	—	34	—	—	34	—	34	—	34	136
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	34
Ab avidity	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	***y***	—	—	0
Specimen storage														
PBMC	CSR		ACD	8.5mL	—	85	—	—	85	—	85	—	85	340
Plasma	CSR		ACD	8.5mL	—	z	—	—	z	—	z	—	z	0
Serum	CSR		SST	8.5mL	—	17	17	—	17	—	17	17	17	102
Visit total					**25**	**255**	**27**	**0**	**275**	**10**	**265**	**45.5**	**258**	**1160.5**
56-Day total					**25**	**280**	**307**	**307**	**302**	**10**	**275**	**45.5**	**258**	
URINE COLLECTION														
Urine dipstick[10,11]	Local lab	Local lab			X	—	X	—	—	—	X	—	—	
Pregnancy test[8,11]	Local lab	Local lab			X	X	—	X	—	X	—	X	—	

Appendix E Laboratory procedures (2 of 2)

Footnotes

[1]CSR = Central Specimen Repository; UW-VSL = University of Washington Virology Specialty Laboratory (Seattle, Washington, USA).

[2]HVTN Laboratories include Fred Hutchinson Cancer Research Center (Seattle, Washington, USA); Duke University Medical Center (Durham, North Carolina, USA).

[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 9.4 (postenrollment).

[6]Immunogenicity assays will be performed at M0, M2.5, M6.5, M9, and M12. 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 (ie, assigned female sex at birth), pregnancy test must be performed on urine or blood specimens within 24 hours of vaccination with negative results received prior to vaccination. Persons who have 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 who is not HIV-infected (see Section 9.11), blood should be drawn for HIV diagnostic testing, as shown for visit 9 above. If a participant has a confirmed diagnosis of HIV infection, do not collect blood for HIV diagnostic testing (see Section 9.13).

[10]And microscopy if needed.

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

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

z = 5 x 1mL aliquots of ACD plasma will be harvested for storage during PBMC processing; no separate blood draw is needed.

Appendix F Procedures at HVTN CRS

Visit:	01[1]	02[11]	03	04	05	06	07	08	09	Post
Day:		D0	D14	D56	D70	D168	D182	D273	D364	
Month:		M0	M0.5	M2	M2.5	M6	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	X	X	X	X	X	X	—	—
Risk reduction counseling[3]	X	X	X	X	X	X	X	X	X	—
Pregnancy prevention assessment[4]	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	—
Social impact assessment questionnaire	—	—	—	—	—	X	—	—	X	—
Outside testing and belief questionnaire	—	—	—	—	—	X	—	—	X	—
Concomitant medications	X	X	X	X	X	X	X	X	X	—
Intercurrent illness/adverse experience	—	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[6]										
Urine dipstick	X	—	X	—	—	—	X	—	—	—
Pregnancy (urine or serum HCG)[7]	X	X	—	X	—	X	—	X	—	—
CBC, differential and platelets	X	—	X	—	X	—	X	X	—	—
Chemistry panel (see Sections 9.2, 9.4)	X	—	X	—	X	—	X	X	—	—
Syphilis, Hepatitis B, Hepatitis C	X	—	—	—	—	—	—	—	—	—
Vaccination procedures[8]										
Vaccination[9]	—	X	—	X	—	X	—	—	—	—
Reactogenicity assessments[10]	—	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 transmission risk reduction counseling for HIV-infected participants.
[4] Pregnancy prevention assessment is required only for participants who were assigned female sex at birth and are capable of becoming pregnant.
[5] Includes pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. If a participant has a confirmed diagnosis of HIV infection, do not perform HIV infection assessment.

[6] For participants with a confirmed diagnosis of HIV infection, specimens listed under "Safety labs" in Appendix E, urinalysis, and urine pregnancy tests will be collected per the protocol schedule.
[7] For a participant who was assigned female sex at birth, 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 eligibility may be performed at screening, but must also be done on Day 0 prior to vaccination. Persons who have undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.
[8] Not applicable to HIV-infected participants.
[9] Blood draws required at vaccination visits must be performed prior to vaccination; however, it is not necessary to have results prior to vaccination, except for results of a urine or serum pregnancy test, if indicated.
[10] Reactogenicity assessments performed daily for at least 7 days postvaccination (see Section 9.9).
[11] Specimens indicated for Day 0 may be obtained within the 14 days prior to vaccination, except for a pregnancy test which must be performed on urine or blood specimens within 24 hours of vaccination with negative results received prior to vaccination.

Appendix G Procedures at CRS for health contact

	Contact[1] day: Month:	546 18
Procedures		
Vital status and health events[2]		X

[1] Clinic visits are not required, except that any participant reporting a diagnosis of HIV infection will be asked to come to the clinic so that HIV status can be confirmed.

[2] See Section 9.5

Appendix H Adverse events of special interest

AEs of special interest (AESI) for this protocol include but are not limited to potential immune-mediated diseases; representative examples of AESI are listed below. Updates to AESI will be provided as an appendix to the *HVTN 123 Study Specific Procedures.*

Gastrointestinal disorders	Liver disorders	Metabolic diseases
• Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis	• Addison's disease • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type I • Grave's or Basedow's disease
Neuroinflammatory disorders	**Musculoskeletal disorders**	**Skin disorders**
• Acute disseminated encephalomyelitis, including site specific variants (eg, non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis) • Cranial nerve disorders, included paralyses/paresis (eg, Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Narcolepsy • Optic neuritis • Transverse Myelitis	• Antisynthetase syndrome • Dermatomyositis • Juvenile chronic arthritis (including Still's disease) • Mixed connective tissue disorder • Polymyalgia rheumatic • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis	• Alopecia areata • Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis • Cutaneous lupus erythematosus • Erythema nodosum • Morphoea • Lichen planus • Psoriasis • Sweet's syndrome • Vitiligo
Vasculitides	**Others**	
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg-Strauss syndrome (allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis	• Antiphospholipid syndrome • Autoimmune hemolytic anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Autoimmune myocarditis/cardiomyopathy • Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis	

Appendix I HVTN low risk guidelines for the US

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

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

1. Sexual behaviors

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

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

AND

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

In the **last 6 months**:

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

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

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

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

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

AND

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

2. Non-sexual behaviors

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

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

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

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

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

Appendix J Protocol Signature Page

A phase 1 double-blind, randomized, controlled clinical trial in healthy, HIV-1–uninfected adult participants to compare the safety, tolerability and immunogenicity of CH505TF gp120 produced from stably transfected cells to CH505TF gp120 produced from transiently transfected cells

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 (U.S.) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (eg, U.S. National Institutes of Health, Division of AIDS) and institutional policies

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

DAIDS Protocol Number: HVTN 123

DAIDS Protocol Version: HVTN 123, Version 1.0

Protocol Date: December 12, 2018