

PROTOCOL

HVTN 999

A Phase I Safety and Immunogenicity Trial of an Alphavirus Replicon HIV Subtype C *Gag* Vaccine (CEU101, CEUVax, Inc.) in Healthy HIV-1 Uninfected Adult Volunteers

**[FDA B-IND (#1234567) – held by CEUVax, Inc.]**

**[MCC CTX (# pending) – held by CEUVax, Inc.]**

CLINICAL TRIAL SPONSORED BY

Division of AIDS (DAIDS)

National Institute of Allergy and Infectious Diseases (NIAID)

National Institutes of Health (NIH)

Department of Health and Human Services (DHHS)

Bethesda, Maryland, USA

STUDY PRODUCT(S) PROVIDED BY

CEUVAX, Inc.

Seattle, Washington, USA

, Version 1.0

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# Ethical considerations

Multiple candidate HIV vaccines will need to be studied simultaneously in different populations around the world before a successful HIV preventive vaccine is found. It is critical that universally accepted ethical guidelines are followed at all sites involved in the conduct of these clinical trials. The HIV Vaccine Trials Network (HVTN) has addressed ethical concerns in the following ways:

* HVTN trials are designed and conducted to enhance the knowledge base necessary to find a preventive vaccine, using methods that are scientifically rigorous and valid, and in accordance with Good Clinical Practice (GCP) guidelines.
* HVTN scientists and operational staff incorporate the philosophies underlying major codes [1-3], declarations, and other guidance documents relevant to human subjects research into the design and conduct of HIV vaccine clinical trials.
* HVTN scientists and operational staff are committed to substantive community input—into the planning, conduct, and follow-up of its research—to help ensure that locally appropriate cultural and linguistic needs of study populations are met. Community Advisory Boards (CAB) are required by DAIDS and supported at all HVTN research sites to ensure community input.
* HVTN clinical trial staff counsel study participants routinely on how to reduce HIV risk. Participants who become HIV-infected during the trial are provided counseling on notifying their partners and about HIV infection according to local guidelines. Staff members will also counsel them about reducing their risk of transmitting HIV to others.
* The HVTN requires that all international HVTN sites lacking national plans for providing antiretroviral therapy (ART) develop plans for the care and treatment of participants who acquire HIV infection during a trial. Each plan is developed in consultation with representatives of host countries, communities from which potential trial participants will be drawn, sponsors, and the HVTN. Participants will be referred to programs for ART provision when the appropriate criteria for starting ART are met. If a program 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 recognizes the importance of institutional review and values the role of in country Institutional Review Boards (IRBs) and Ethics Committees (ECs) as custodians responsible for ensuring the ethical conduct of research in each setting.

# IRB/EC review considerations

US Food and Drug Administration (FDA) and other US federal regulations require IRBs/ECs 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 questions or concerns regarding these research requirements.

## 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 women); and (f) providing safety monitoring.

## Reasonable risk/benefit balance

45 CFR 46.111 (a) 2 and 21 CFR 56 (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.

## Equitable subject 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.

## Appropriate informed consent

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

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

## 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 clinical affairs staff and routinely by the Protocol Safety Review Team (PSRT). Site staff have 24-hour cell phone access to clinical affairs staff. In addition, the HVTN Safety Monitoring Board (SMB) or a Data and Safety Monitoring Board (DSMB) periodically reviews study data.

## Protect privacy/confidentiality

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

Privacy refers to an individual’s right to be free from unauthorized or unreasonable intrusion into his/her private life and the right to control access to individually identifiable information about him/her. The term “privacy” concerns research participants or potential research participants as individuals whereas the term “confidentiality” is used to refer to the treatment of information about those individuals. This protocol respects the privacy of participants by informing them about who will have access to their personal information and study data (see Appendix A). The privacy of participants is protected by assigning unique identifiers in place of the participant’s name on study data and specimens. In the United States, research participants in HVTN protocols are protected by a Certificate of Confidentiality from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. Participants are told of the use and limits of the certificate in the study consent form. In addition, each staff member at each study site in this protocol signs a Confidentiality Agreement with the HVTN and each study site participating in the protocol is required to have a standard operating procedure on how the staff members will protect the confidentiality of study participants.

# Overview

Title

A Phase I Safety and Immunogenicity Trial of an Alphavirus Replicon HIV Subtype C *Gag* Vaccine (CEU101, CEUVax, Inc.) in Healthy HIV-1 Uninfected Adult Volunteers

Primary objective

 To evaluate the safety and tolerability of escalating doses of the candidate vaccine.

**Secondary objective**

To evaluate the immunogenicity of escalating doses of the candidate vaccine.

Study products and routes of administration

Vaccine: Alphavirus Replicon HIV Subtype C Gag Vaccine (CEU101, CEUVax, Inc.)

Control: phosphate buffered saline

Administration: Intramuscular injection with needle and syringe, 0.5 mL in the deltoid muscle

Table ‑ Schema

Vaccination schedule in months (days)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | US | S. Africa |  |  |  |  |  |  |
| Study arm | Number | Number |  | Dose |  | 0 (0) | 1 (28) | 3 (84) |
|  |  |  |  |  |  |  |  |  |
| Group 1 | 10 | 10 |  | 0.5 mL (1x104) |  | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | 0.5 mL |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |  |  |
| Group 2 | 10 | 10 |  | 0.5 mL (1x105) |  | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | 0.5 mL |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |  |  |
| Group 3 | 10 | 10 |  | 0.5 mL (1x106) |  | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | 0.5 mL |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |  |  |
| Group 4 | 10 | 10 |  | 0.5 mL (1x107) |  | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | 0.5 mL |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |  |  |
| Total | 48 (40/8) | 48 (40/8) |  |  |  |  |  |  |

Note: Enrollment in Groups 1-4 will occur sequentially.

Participants

96 healthy, HIV-1–uninfected volunteers aged 18 to 50 years; 80 vaccinees, 16 control recipients divided evenly between the US and South Africa

Design

Multicenter, randomized, controlled, double-blind trial

Duration per participant

12 months of scheduled clinic visits (main study)

Estimated total study duration

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

Investigational New Drug (IND) sponsor

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

Core operations

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

Statistical and data management center (SDMC)

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

HIV diagnostic laboratory

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

Endpoint assay laboratories

* Duke University Medical Center (Durham, North Carolina, USA)
* FHCRC/University of Washington (Seattle, Washington, USA)
* South Africa Immunology Laboratory and National Institute for Communicable Diseases (Johannesburg, South Africa)

Study sites

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

Safety monitoring

HVTN 999 PSRT; HVTN Safety Monitoring Board (SMB)

## Protocol Team

Protocol leadership

|  |  |  |  |
| --- | --- | --- | --- |
| Chair | Curious George, MD,University of Rochesterxxx-xxx-xxxxemail | Statistician | Cary Grant, PhDSCHARPxxx-xxx-xxxxemail |
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| Protocol Team leader | Dr. Jim Maynard, MBChB, DHSM, FCCHHVTN Corexxx-xxx-xxxxemail |  |  |

Other contributors to the original protocol

|  |  |  |  |
| --- | --- | --- | --- |
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# Background

## Rationale for trial concept

The ongoing worldwide epidemic of the human immunodeficiency virus type 1 (HIV-1) remains one of the major global health challenges. HIV-1 causes the acquired immunodeficiency syndrome (AIDS), which is responsible for tremendous human suffering and economic loss throughout the world. Currently, over 39 million people are living with HIV-1 infection [1]. Without treatment, it is likely that nearly all of these will die of AIDS in the next 2 decades.

Since 1996, potent new antiretroviral therapies, including combination regimens with protease inhibitors, have created the possibility that HIV-1 infection might become a chronic, manageable disease among individuals with access to these medications. In the US, AIDS deaths are down to 18,000 per year as a result of the new antiretrovirals [2]. However, for the developing world, where over 98% of the nearly 5 million annual incident HIV-1 infections occur [1], it is unlikely that these drugs will be widely accessible, due to many logistical challenges associated with their use.

Globally, 13,000 new infections occur each day. More than 3 million AIDS deaths occur per year [1], and nearly 20 million have died since the HIV epidemic began [3]. AIDS has become the leading infectious disease killer, the fourth leading cause of death overall. In severely affected countries, life expectancy has fallen by more than 10 years [1]. AIDS is the leading killer in Africa, with over 25 million Africans living with HIV/AIDS. Sub-Saharan Africa has been affected most; in 7 Sub-Saharan African countries, over 22 million adults (aged 15-49) are living with HIV/AIDS [3]. For example, in Botswana, 37.3% of adults aged 15 to 49 are infected with HIV, while in South Africa more than 25% of women in antenatal clinics are infected [3].

After sub-Saharan Africa and Asia, Latin America is the region most severely affected by HIV infection. The HIV epidemic in Latin America reflects diverse transmission patterns: in Andean countries HIV is most often transmitted sexually, primarily among men who have sex with men (MSM), while in Brazil, Uruguay and Argentina a significant proportion (39% of AIDS cases in Argentina) of HIV transmission occurs through injection drug use (IDU). In all countries of the Andean Region, MSM account for a substantial proportion of HIV infections and comprise a “bridge” group for spread into the heterosexual population due to the high frequency of bisexuality. HIV incidence is higher among high-risk MSM in Brazil and Peru compared to most U.S. populations [4-9].

The need for better education, better treatment access, better prevention programs, and better prevention technologies is therefore clear. Specifically, the need for a safe, effective, and affordable HIV-1 vaccine is paramount [10,11]. The ideal HIV-1 vaccine for global use should meet several of the following criteria:

* proven safety in healthy HIV-uninfected persons
* induction of long-lasting HIV-specific cell-mediated and humoral immunity capable of conferring protection against HIV
* tolerability
* potential for production in sufficient quantity to meet global needs
* affordability
* stability during distribution and storage

## CEU101

CEUVax, Inc. uses a propagation-defective, alphavirus replicon vector system, derived from an attenuated strain of Cascadian ursus virus virus (CUV), to design, engineer, and test in humans a vaccine for HIV. The vector system is derived from a CUV virus that has been genetically modified to be avirulent. The structural protein genetic region of this avirulent strain has been excised and can be replaced by a heterologous gene of interest. The resulting RNA construct is called a replicon because, when introduced into a cell, it replicates within the cell and expresses the heterologous gene product. Vaccine is produced by simultaneous co‑transfection of cell cultures with replicon RNA transcripts, along with two additional RNA transcripts encoding the structural genes of an attenuated CUV virus, leading to the production of virus-like particles. These single-cycle vaccine replicon particles (VRP) can efficiently infect cells *in vitro* or *in vivo* and express the heterologous gene product, but they are designed to be defective in their ability to propagate and to prevent the formation of new virus-like particles that could infect new cells.

## Trial design rationale

The first investigational alphavirus replicon vaccine (CEU101) contains a replicon expressing the *gag* gene from a South African subtype C isolate of HIV-1. This investigational product is utilized for the purpose of establishing a safety profile for an alphavirus replicon vaccine in healthy human participants.

Several live recombinant vectors such as pox viruses and bacteria expressing multiple HIV-1 genes have been tested in animals and humans. They have been shown to be safe and immunogenic, but induce only weak to moderate HIV-specific immune responses. CEUVax, Inc. has developed a novel vaccine vector based on CUV.[[1]](#endnote-1) Propagation-incompetent replicon particles have been genetically engineered to encode specific genes of interest. Upon vaccination, VRP carry the gene into cells *in vivo*, leading to expression of antigenic proteins. VRP can target antigen presenting cells *in vivo* and are capable of inducing a broad array of immune responses to the relevant gene product, including cytotoxic T lymphocytes (CTL), lymphoproliferative responses, and neutralizing antibodies, with little or no immune response to CUV. Moreover, VRP can confer protection in animal models against several diseases such as those caused by influenza, Ebola, or Marburg viruses.[[2]](#endnote-2),[[3]](#endnote-3),[[4]](#endnote-4)

More recently, vaccine vectors derived from CUV that expressed simian immunodeficiency virus (SIV) immunogens were tested in rhesus macaques as part of the effort to design a safe and effective vaccine for human immunodeficiency virus.[[5]](#endnote-5) Immunizations with VRP induced both humoral and cellular immune responses. Four of four vaccinated animals were protected against disease for at least 16 months following intravenous challenge with a pathogenic SIV swarm, while two of four control animals required euthanasia at 10 and 11 weeks. Vaccination reduced the mean peak viral load 100‑fold. The plasma viral load was reduced to below the limit of detection (1500 genome copies/mL) in one vaccinated animal between 6 and 16 weeks postchallenge and in another from week 6 through the last sampling time (40 weeks postchallenge). The extent of reduction in challenge virus replication was directly correlated with the strength of the immune response induced by the vectors.

Based on the above data, an alphavirus replicon vaccine expressing the *gag* gene from a South African subtype C isolate of HIV-1 (CEU101) was evaluated in preclinical studies. Immunization of mice with two injections of CEU101 (105 IU by subcutaneous footpad inoculation) induced a Gag‑specific antibody response as measured by ELISA, and a Gag‑specific CD8+ T cell response as measured by 51Cr-release CTL assay or ELISPOT assay. This is the product that will be evaluated in a Phase I clinical trial under the current protocol.

Following establishment of safety of this first investigational product (CEU101), the next investigational product will be formulated as a multi-antigen vaccine, containing VRP expressing three HIV genes, *gag*, *pol* and *env*, derived from subtype C viruses. These HIV viruses were isolated from likely Phase III trial sites in South Africa in collaboration with South African scientists.

Given the current state of knowledge regarding correlates of protection against HIV/AIDS, this candidate vaccine strategy is attractive because of the magnitude and breadth of specific immune responses elicited by VRP in a variety of disease models.

## Preclinical studies

##

## 4.4.1 Humoral Immune Responses

Immunization of mice and rabbits with CEU101 consistently induced a Gag‑specific antibody response as measured by ELISA.

When mice received two doses of 105 IU CEU101 by subcutaneous footpad injection on Day 0 and Day 21, the geometric mean reciprocal antibody titer was 4200 or 5583 for two pilot lots of vaccine and 5747 or 6451 for two GMP lots of vaccine.

Rabbits received three injections of 104, 106 or 107 IU CEU101 or a vehicle control by subcutaneous injection in the distal forelimb at 3‑week intervals. At the 106 IU dose, seroconversion occurred in 5 of 12 rabbits by 3 weeks after the second dose and in all animals tested at 2 weeks after the third dose. At the 107 IU dose, seroconversion occurred in 10 of 12 rabbits by 3 weeks after the second dose and in all animals tested at 2 weeks after the third dose. The final antibody titer was higher in animals that received the 107 IU dose (GMT = 1140) than in animals who received the 106 IU dose (GMT = 508).

##

## 4.4.2 Cellular Immune Responses

Immunization of mice with CEU101 consistently induced cellular immune responses as measured in a variety of assays.

In a standard 51Cr-release assay of spleen cells harvested from mice immunized with two doses of 105 IU CEU101 by subcutaneous footpad injection, a Gag‑specific CTL response was observed for cells stimulated *in vitro* with either a recombinant vaccinia expressing an HIV subtype C *gag* gene or with an H-2Kd-restricted Gag peptide.

When spleen cells from mice immunized with two doses of 105 IU CEU101 by subcutaneous footpad injection were stimulated *in vitro* with an H-2Kd -restricted Gag peptide, a Gag‑specific CD8+ T‑cell response was observed in an IFN- ELISPOT assay.

As an indicator of CD4+ T‑cell subset responses, antigen‑specific IgG2a and IgG1 ELISA assays were performed on sera from mice immunized with two doses of 105 IU of CEU101. A Th1‑type response was observed in more than 75% of mice immunized with CEU101. The mean (± SE) IgG2a/IgG1 ratio was 4.4 ± 1.1.

## 4.4.3 Rabbit Toxicology Study

A formal toxicology study in rabbits showed no systemic toxicity or other unexpected effects related to CEU101.

Three groups of 12 New Zealand white rabbits (six male and six female) were inoculated subcutaneously with 104, 106, or 107 IU of CEU101. A negative control group received the vehicle only. Animals received three injections at Weeks 0, 3 and 6. Half of the animals were sacrificed 2 days after the last injection (Week 6) and the other half 2 weeks after the last injection (Week 8).

Systemic toxicity was evaluated by recording mortality/morbidity, body temperature, body weight, food consumption and ophthalmic examinations. Hematopoietic toxicity was evaluated by quantitating cellular components of peripheral blood. Immune system toxicity was assessed by histopathologic evaluation of the lymphoid organs. Other organ toxicity was assessed by monitoring clinical chemistry parameters. Local reactogenicity was evaluated by examining the injection sites grossly and microscopically to determine irritation potential.

Physical examination of the injection site showed minimal erythema or edema, which resolved within 1-2 days, in approximately one‑third of the animals in each of the four groups. Histopathologic examination of the injection site 2 days after the last inoculation showed a local inflammatory response in most animals in all groups. The local inflammatory response was minimal to mild in the 104 IU, 106 IU and vehicle control groups and mild to marked in the 107 IU group, and had decreased in severity by 2 weeks after inoculation. There was no evidence of systemic, hematopoietic, immune system or other organ toxicity related to CEU101.

*(Refer to the Investigator’s Brochure for further information about nonclinical studies with CEU101.)*

## Clinical studies

No previous clinical studies of CEU 101 have been performed.

## Potential risks of study products and administration

Table ‑ Summary of potential risks of study products and administration

|  |  |
| --- | --- |
| Common | * Mild to moderate injection site pain, tenderness, erythema, or swelling/induration/edema
* Malaise/fatigue, myalgia, or headache in the first few days following injection
* A vaccine-induced positive HIV antibody test result
 |
| Less common | * Severe injection site pain or tenderness
* Fever, chills, flu-like syndrome, arthralgia, rash, nausea, or dizziness in the first few days following injection
* Vasovagal reaction/lightheadedness/dizziness related to the injection procedure
* Transient changes in clinical laboratory values
* Injection site hematoma, bruising/ecchymosis, laceration, other transient lesions, 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
 |
| Unknown frequency or theoretical risks | * Muscle damage at the injection site
* Autoimmune disease or cancer
* 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
 |

# Objectives and endpoints

## Primary objectives and endpoints

Primary objective 1:

To evaluate the safety and tolerability of escalating doses of CEU101.

Primary endpoint 1:

Local and systemic reactogenicity signs and symptoms, laboratory measures of safety, and adverse and serious adverse events.

## Secondary objectives and endpoints

Secondary objective 1:

To evaluate the immunogenicity of escalating doses of the candidate vaccine.

Secondary endpoint 1:

* Response rate and magnitude of HIV-specific CD8+ T-cell responses at 24 weeks after the second third vaccination.
* Avidity indices for Env-specific binding antibodies measured 2 and 24 weeks following the final vaccination

## Exploratory objectives

Exploratory objective 1:

To further characterize the effector and memory cell phenotypes and functional profiles of HIV-specific CD4+ and CD8+ T cells in participants

Exploratory objective 2:

To further characterize antibody responses and to characterize the frequency of antibody-secreting B cells (ASCs; plasmablasts) and memory B cells in participants

*Exploratory objective 3:*

To characterize the frequency of responding follicular helper T cells (TFH) in participants

*Exploratory objective 4:*

To characterize the magnitude and frequency of regulatory T cells (TREG) in peripheral blood of participants

*Exploratory objective 5:*

To characterize transcriptional profiles relating to T-cell differentiation in participants

# Statistical considerations

## Overview

This study is a multicenter, randomized, placebo-controlled, double-blind trial. The data analysis will evaluate safety and immunogenicity data in the study groups.

#### **Power Calculations**

For each dose level, 20 participants receive the vaccine. If the true rate of occurrence of a given toxicity is less than 5%, then the probability that two or more events are observed among the 20 participants is less than 26%. Based on data from 20 vaccinees, the probability of discontinuing the dose escalation is 61%, 93%, and 99% when the rate of true toxicity is 10%, 20%, or 30%, respectively.

In the event that the dose-escalation is performed within one country, then 10 participants receive the vaccine at each dose level. In this case, if the true rate of occurrence of a given toxicity is less than 5%, then the probability that two or more events are observed among the 10 participants is less than 9%. Based on data from 10 vaccinees, the probability of discontinuing the dose escalation is 26%, 62%, and 85% when the rate of true toxicity is 10%, 20%, or 30%, respectively.

## Objectives

The primary objectives are defined in Section 6.1, the secondary objectives in Section 6.2.

## Endpoints

### Safety

Assessment of product safety will include clinical observation and monitoring of hematological and chemical parameters. Safety will be evaluated by monitoring participants for local and systemic adverse reactions after each injection and for 12 months after the first injection.

The following parameters will be assessed:

* Local reactogenicity signs and symptoms
* Systemic reactogenicity signs and symptoms
* Laboratory measures of safety
* Adverse events

### Immunogenicity

Primary immunogenicity endpoints are:

* Primary endpoints measure safety of the candidate vaccine given in escalating doses. Toxicities of the candidate vaccine at different dose levels are measured by local and systemic reactions to vaccination, and by laboratory assessment parameters listed in Section **Error! Reference source not found.**. The timing of measurement of the safety variables is given in Appendix D.
* Adverse Events and Serious Adverse Events
* The severity of illnesses and adverse experiences are categorized using a standard grading scale with the following severity levels: none, mild, moderate, severe, life-threatening, and death. The relationship of these events to vaccination will be assessed and documented by the investigator/clinician. Safety of the candidate vaccine will be assessed primarily by the occurrence of Grade 3 (Severe) or Grade 4 (Life-threatening) adverse events deemed to be probably or definitely related to the vaccine. Grade 1 (Mild) and Grade 2 (Moderate) adverse experiences will also be analyzed.
* Adverse experiences will be judged as Serious Adverse Experiences (SAEs) using the criteria given by the Division of AIDS (DAIDS) SAE Reporting Manual for HIV Vaccine Trials Network (HVTN).
* Severity of Vaccine Reactions
* The severity of local and systemic reactions to vaccine is categorized using a standard grading scale with the following levels: none, mild, moderate, severe (see Appendix G).
* Local vaccine reactions will include pain, tenderness, erythema and induration.
* Systemic vaccine reactions will include malaise, fatigue, chills, headache, myalgia, arthralgia, nausea, and vomiting.
* Temperature
* Temperature is measured before and after each vaccination, and approximately 25-45 minutes post-vaccination. In addition, temperature is measured by participants daily for 7 days following each vaccination.
* Cell Counts and Chemistries
* Measurements of absolute CD8+ and CD4+ T cells, and platelet counts.

Secondary immunogenicity endpoints are:

* Secondary endpoints measure immunogenicity of the vaccine given in escalating doses. Immunogenicity will be assessed by humoral and cellular immune responses.
* Humoral immune response of the candidate vaccine at different dose levels is measured by ELISA-based assays of binding antibodies to HIV-1 Gag and antibodies to CUV will be measured by a VRP neutralization assay. Cellular immune response will be assessed by 51Cr-release CTL, by IFN-γ ELISPOT and flow-cytometry-based assays of CD8+ and CD4+ cellular responses to HIV-1 subtype C Gag; and by lymphocyte proliferation assays (LPA) in response to HIV-1 subtype C Gag. (see Section **Error! Reference source not found.**for a list of the assays used).

### Social impacts

Social impact variables include any negative experiences or problems the participant experienced due to his/her participation in this study. The following social impacts will be followed during the course of the study: social, travel, work, school, health care, life insurance, health insurance, housing, military and any additional impacts identified by a participant.

## Accrual and sample size

Recruitment will target 96 healthy, HIV-uninfected adult participants. Participants will be healthy HIV-1 uninfected (seronegative) adults who comprehend the purpose, the possible risks and benefits, and other details of the study. Risk status for HIV infection will be determined by a prescreen series of questions designed to identify risk factors for HIV-1 infection. Enrollment into the protocol will be limited to those adult participants (male and female). After participants sign the consent form for pretrial eligibility tests, investigators will proceed with phlebotomy, medical history, physical examination, and final questions regarding sexual behavior and other practices. Eligibility determination for the trial will be dependent on results of physical exam, laboratory tests and answers to the self-administered and/or interview questions.

### Sample size calculations for safety

The goal of the safety evaluation for this study is to identify safety concerns associated with administration. Sample size calculations for safety are expressed in terms of the ability to detect rare events.

The ability of the study to identify rare events can be expressed by the maximum true rate of events that would be unlikely to be observed and the minimum true rate of events that would very likely be observed.

### Sample size calculations for immunogenicity

The main goals of this trial regarding immunogenicity outcomes involve a preliminary estimation of response rates. The precision with which response rates can be estimated, based on a sample of 96 vaccinees, accounting for 10% missing immunogenicity data, is limited. The standard error of the estimated response rates depends on the true underlying response rate but can be bounded by 96 (= ). Thus, the width of a 95% confidence interval, using a normal approximation method to calculate the width, for the response rate in any 1 arm will be no greater than 4 (ie, ±1.96 x 2).]

Exact 2-sided confidence intervals for the response rate based on observing a particular rate of responses in the vaccinees is shown in Table 1-3.

An alternative to formal comparisons of arms is to rank the arms by their response rates. For arms of size n, we can assess the reliability of this study to select the best arm with respect to the magnitude of response rates. Table 1-5 shows various true response rates for which this study will correctly select the arm with highest response rate with high probability. Each line in the table shows the results based on 40,000 simulated datasets generated using 2 (best/next best) different binomial probabilities for k arms of size n, with the best (highest) response probability used to generate data for one arm and the next best (low) response probability used to generate data for the remaining (k–1) arms [12]. If the difference in response between the best and next best arms is smaller than the assumed difference, the chance of correctly selecting the arm with the true highest response will be less than 80% (90%).

## Statistical analysis

All data from enrolled participants will be analyzed according to the initial randomization assignment regardless of how many vaccinations they received. Since enrollment is concurrent with receiving the first vaccination, all participants will have received one vaccination and therefore will provide some safety data. The analysis is not strictly intent-to-treat but is approximately so; however, 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, according to the *HVTN Manual of Operations* (HVTN MOP) (Study Operations >Enrollment >Randomization)—very few such individuals are expected.

If a participant receives the wrong randomization assignment, analyses for immunogenicity will be done both according to the assignment they should have received as well as according to the assignment they actually received. It is expected that there should be very few such cases.

Analyses for primary endpoints will be performed in SAS. All other descriptive and inferential statistical analyses will be performed using SAS, S-Plus, and/or R statistical software.

No formal multiple comparison adjustments will be employed for safety endpoints or primary immunogenicity endpoints that address specified scientific questions (eg, humoral- and cellular-based endpoints), or secondary endpoints. However, multiple measurements of a specific type of immune response may be treated as a collection of hypotheses that requires a multiplicity adjustment. For example, determination of cellular immune responses to several different HIV-1 peptide pools as measured by the IFN-γ ELISpot assay may entail a multiplicity adjustment to account for the multiple peptide pools considered.

### Analysis variables

The analysis variables consist of baseline variables, safety variables, immunogenicity variables, and social impact variables for primary and secondary objective analyses.

### Baseline comparability

Groups will be compared for baseline characteristics including demographics and laboratory measurements, using descriptive statistics.

### Safety analysis

*Reactogenicity*

The number and percentage of participants experiencing each type of reactogenicity sign or symptom will be tabulated by severity. For a given sign or symptom, each participant’s reactogenicity will be counted once under the maximum severity for all injection visits.

*Adverse experiences*

Adverse experiences will be analyzed using MedDRA preferred terms. The number and percentage of participants experiencing each specific adverse experience will be tabulated by severity and by relationship to treatment. For the calculations in these tables, each participant’s adverse experience will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

A listing of expedited adverse events reported to the DAIDS Safety Office will provide details of the event including severity, relationship to study product, onset, duration and outcome.

*Local laboratory values*

Boxplots of local laboratory values will be generated for baseline values and for values measured during the course of the study. Each boxplot will show the 1st quartile, the median, and the 3rd quartile. Outliers, or values outside the boxplot, will also be plotted. If appropriate, horizontal lines representing boundaries for abnormal values will be plotted.

### Immunogenicity analysis

For the statistical analysis of immunogenicityendpoints, all data from enrolled participants will be used according to the initial randomization assignment regardless of how many injections they received. The only exception will be to exclude data from HIV-infected participants at or post infection. Thus, for HIV-infected participants, only immunogencity data from samples drawn prior to HIV infection will be included in the analysis.

If assay data are qualitative (ie, positive or negative) then analyses will be performed by tabulating the frequency of positive response for each assay by arm at each time point that an assessment is performed. Binomial response rates will be presented with their corresponding exact 95% confidence interval estimates. Because of the small numbers of control participants in each group, no adjustment will be made to the vaccine arm estimates for the false positive rates in the control arms.

To compare the response rates of any two vaccine arms, a significant difference will be declared if the 2-sided 95% confidence interval for the difference in response rates between the two arms excludes 0. If assays are run at multiple time points, the probability of observing at least one positive response by a given time point and the probability of observing more than one response by a given time point will be estimated, with corresponding confidence intervals, for each vaccine arm using maximum likelihood based methods [13]. Missing responses will be assumed to be missing at random, ie, conditional on the observed data the missingness is independent of the unobserved responses.

For continuous assay variables, overall differences between arms at a specific time point will be tested by a 2-sample t-test if the data appear to be normally distributed, or by utilizing the nonparametric Wilcoxon rank sum test if the data are not normally distributed. If a portion of the measurements are censored below the assay quantification limit, then the Gehan-Wilcoxon test will be employed. More sophisticated analyses employing repeated measures methodology (for example, repeated measures ANOVA or generalized estimating equations) may be utilized to incorporate immune responses over several time points. However, inference from such analyses would be limited by the small sample size of this study. All statistical tests will be 2-sided and will be considered statistically significant if p ≤ 0.05. Graphical descriptions of the longitudinal immune responses will also be given.

Some immunologic assays have underlying continuous or count-type readout that is often dichotomized into responder/nonresponder categories. For these assays, graphical and tabular summaries of the underlying distributions will be made. These summaries may be performed on transformed data (eg, log transformation) to better satisfy assumptions of symmetry and homoscedasticity. If arm comparisons in these underlying distributions reveal that differences are best summarized as a shift in the location of the distribution, then results will be presented in the form of arm means (or medians) with associated confidence intervals and statistical tests for differences between arms as described above. If arm comparisons in these underlying distributions reveal that differences are best summarized by a mixture model (ie, responder and nonresponder subgroups are clearly identifiable), then results will be presented in the form of response rates with associated confidence intervals and statistical tests as described above. In addition, Lachenbruch’s test statistic [14] will be used for evaluating the composite null hypothesis of equal response rates in the two arms and equal response distributions among responders in the two arms. This test statistic equals the square of a binomial Z-statistic for comparing the response rates plus the square of a Wilcoxon statistic for comparing the response distributions in the subgroup of responders. A permutation procedure is used to obtain a 2-sided p-value.

#### **Missing data**

If the probability of missing immunogenicity measurements depends on either covariates or on the immunogenicity outcomes of participants, then the methods described above may give biased inferences and point estimates. If a substantial amount of immunogenicity data are missing (at least 1 value missing from more than 20% of participants), then secondary analyses of the immunogenicity endpoints will be conducted using methods that relax the missing completely at random assumption to a missing at random assumption. For a univariate binary and quantitative outcome, respectively, a generalized linear model with a binomial or normal error distribution will be used for estimation and testing. For assessing repeated immunogenicity measurements, generalized estimating equations models with multiple imputation of missing responses will be used. The models will include as covariates all available baseline predictors of the missing outcomes. The longitudinal models will also include all observed immunogenicity data.

### Social impact descriptive analysis

Social impacts will be tabulated by type of event and impact on quality of life. The number and percentage of participants experiencing each type of social impact will also be tabulated by impact on quality of life. For this calculation multiple events of the same type for a participant will be counted once under the maximum impact for all post-vaccination visits.

In addition, a listing will be generated of all participants who experienced a major disturbance of their quality of life due to study participation. The listing includes all social impacts experienced by these participants, descriptions of each impact, duration, impact on quality of life, actions taken by the participant and staff, and whether or not there was a resolution.

### Analyses prior to end of study

*Safety*

During the course of the trial, unblinded analyses of safety data are prepared every four months for review by the Safety Monitoring Board (SMB). Unblinded ad hoc safety reports may also be prepared for SMB review at the request of the Protocol Safety Review Team. The SDMC Director (or designee) and the HVTN Director (or designee) must approve any other requests for unblinded safety data prior to the end of study.

*Immunogenicity*

An unblinded statistical analysis of an immunogenicity endpoint may be performed when the Laboratory Program has completed testing of all samples from the primary immunogenicity visit. The Laboratory Program will review the analysis report prior to distribution to the protocol chairs, DAIDS, vaccine developer, and other key HVTN members and investigators. Distribution will be limited to those with a need to know for the purpose of informing future trial-related decisions. The SDMC Director (or designee) and the Lab Program Director (or designee) must approve any other requests for immunogenicity analyses prior to the end of the study. Any analyses conducted prior to the end of the study should in no way compromise the integrity of the trial in terms of participant retention or safety or immunogenicity endpoint assessments.

## Randomization of treatment assignments

The randomization sequence will be obtained by computer-generated random numbers and provided to each HVTU using standard SDMC procedures*.* Permuted blocks of size 6 (5 active,1 placebo) will be used. The randomization code is kept at each institution by the pharmacist of record with primary responsibility for drug dispensing. Vaccine preparations will be provided to the investigators and clinic staff in a blinded fashion by the HVTU pharmacist. Unblinding will occur at the end of the study following standard HVTN policy.

# Selection and withdrawal of participants

Participants will be healthy, HIV-1–uninfected (seronegative) adults who comprehend the purpose of the study and have provided written informed consent. Volunteers will be recruited and screened; those determined to be eligible, based on the inclusion and exclusion criteria, will be enrolled in the study. Final eligibility determination will depend on results of laboratory tests, medical history, physical examinations, and answers to self-administered and/or interview questions.

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

## 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 annually** after completion of scheduled clinic visits for a total of 5 years following initial study injection.
6. **Agrees not to enroll in another study** of an investigational research agent
7. **Good general health** as shown by medical history, physical exam, and screening laboratory tests

HIV-Related Criteria:

1. Willingness to receive **HIV test results**
2. Willingness to discuss **HIV infection risks**, amenable to **HIV risk reduction counseling**, and committed to maintaining behavior consistent with low risk of HIV exposure through the last required protocol clinic visit
3. Assessed by the clinic staff as being at **“low risk” for HIV infection**

Laboratory Inclusion Values

Hemogram/CBC

1. **Hemoglobin** ≥ 11.0 g/dL for volunteers who were born female, ≥ 13.0 g/dL for volunteers who were born male
2. **White blood cell count** = 3,300 to 12,000 cells/mm3
3. **Total lymphocyte count** ≥ 800 cells/mm3
4. **Remaining differential** either within institutional normal range or with site physician approval
5. **Platelets** = 125,000 to 550,000/mm3

Chemistry

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

Virology

1. **Negative HIV-1 and -2 blood test**: US volunteers must have a negative FDA-approved enzyme immunoassay (EIA). Non-US sites may use locally available assays that have been approved by HVTN Laboratory Operations.
2. **Negative Hepatitis B surface antigen (HBsAg)**
3. **Negative anti-Hepatitis C virus antibodies (anti-HCV)**, or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive

Urine

1. **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

1. **Volunteers who were born female**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test performed prior to vaccination on the day of initial vaccination
2. **Reproductive status**: A volunteer who was born female must:
* Agree to consistently use effective contraception (see Appendix B) for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit. Effective contraception is defined as using any of the following methods:
* Condoms (male or female) with or without a spermicide,
* Diaphragm or cervical cap with spermicide,
* Intrauterine device (IUD),
* Hormonal contraception, or
* Successful vasectomy in the male partner (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy);
* Or 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.
1. **Volunteers who were born female must also agree not to seek pregnancy through alternative methods**, such as artificial insemination or in vitro fertilization until after the last required protocol clinic visit

## 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 during the planned duration of the HVTN 999 study
5. **Pregnant or breastfeeding**

Vaccines and other Injections

1. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 999 PSRT will determine eligibility on a case-by-case basis.
2. **Non-HIV experimental vaccine(s) received within the last 5 yea**rs in a prior vaccine trial. Exceptions may be made for vaccines that have subsequently undergone licensure by the FDA. For volunteers who have received control/placebo in an experimental vaccine trial, the HVTN 999 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 999 PSRT on a case-by-case basis.
3. **Live attenuated vaccines** other than influenza vaccine received within 30 days before first vaccination or scheduled within 14/28 days after injection (eg, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever)
4. **Influenza vaccine or any vaccines that are not live attenuated vaccines** and were received within 14 days prior to first vaccination (eg, tetanus, pneumococcal, Hepatitis A or B)
5. **Allergy treatment with antigen injections** within 30 days before first vaccination or that are scheduled within 14 days after first vaccination

Immune System

1. **Immunosuppressive medications** received within 168 days before first vaccination. (Not excluded: [1] corticosteroid nasal spray; [2] inhaled corticosteroids; [3] topical corticosteroids for mild, uncomplicated dermatitis; or [4] a single course of oral/parenteral corticosteroids at doses < 2 mg/kg/day and length of therapy < 11 days with completion at least 30 days prior to enrollment.
2. **Serious adverse reactions to vaccines** including anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain. (Not excluded: a volunteer who had a nonanaphylactic adverse reaction to pertussis vaccine as a child.)
3. **Immunoglobulin** received within 60 /90 days before first vaccination
4. **Autoimmune disease**
5. **Immunodeficiency**

Clinically significant medical conditions

1. **Untreated or incompletely treated syphilis infection**
2. **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.
1. **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
2. **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.
3. **Current anti-tuberculosis (TB) prophylaxis or therapy**
4. **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.
1. **Diabetes mellitus** type 1 or type 2, including cases controlled with diet alone. (Not excluded: history of isolated gestational diabetes.)
2. **Thyroidectomy, or thyroid disease** requiring medication during the last 12 months
3. **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.
1. **Bleeding disorder** diagnosed by a doctor (eg, factor deficiency, coagulopathy, or platelet disorder requiring special precautions)
2. **Malignancy** (Not excluded: 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)
3. **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.
4. **Asplenia**: any condition resulting in the absence of a functional spleen
5. History of hereditary **angioedema**, acquired angioedema, or idiopathic angioedema.

## Participant departure from vaccination schedule or withdrawal

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

### Delaying vaccinations for a participant

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

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

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

In order to avoid vaccination delays and missed vaccinations, participants who plan to receive licensed vaccines, 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 thee interval between a study vaccination and completion of the postvaccination follow-up visit.

### 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).

### 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 999 PSRT).
* Clinically significant condition (ie, a condition that affects the immune system or for which continued vaccinations and/or blood draws may pose additional risk), including but not limited to the following:
* Pregnancy (regardless of outcome);
* Any grade 4 local or systemic reactogenicity symptom, lab abnormality, or AE that is subsequently considered to be related to vaccination;
* Any grade 3 lab abnormality or other clinical AE (exception: fever or vomiting and subjective local and systemic symptoms) that is subsequently considered to be related to vaccination; or
* Clinically significant type 1 hypersensitivity reaction associated with study vaccination. Consultation with the PSRT is required prior to subsequent vaccinations following any type 1 hypersensitivity reaction associated with study vaccination; or
* Investigator determination in consultation with Protocol Team leadership (eg, for repeated nonadherence to study staff instructions).
* Participant misses more than 1 vaccinations(s) (see Section 7.3.2).

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

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

### Participant termination from the study

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

* Participant refuses further participation,
* Participant relocates and remote follow-up or transfer to another HVTN CRS is not possible,
* HVTN CRS determines that the participant is lost to follow-up,
* Participant becomes HIV infected, 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.

# Study product preparation and administration

HVTU pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networksmanual for standard pharmacy operations procedures. The protocol schema and vaccine regimen are shown in Section . See the Investigator’s Brochure for further information about study products.

## Schema and vaccine regimen

Vaccine: Alphavirus Replicon HIV Subtype C Gag Vaccine (CEU101, CEUVax, Inc.)

Placebo: phosphate buffered saline

Administration: Intramuscular injection with needle and syringe, 0.5 mL in the deltoid muscle

Table 13-1: Administration Schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Treatment Assignment** | **Vaccine Dose(IU)** | **InjectionSite** |  **Vaccination Schedule in Days** |
| **0** | **28** | **84** |
| I | T1 | 0.5 mL(1 x 104) | Deltoid (SC) | CEU101 | CEU101 | CEU101 |
| P1 | 0.5 mL | Deltoid (SC) | Placebo | Placebo | Placebo |
| II | T2 | 0.5 mL(1 x 105) | Deltoid (SC) | CEU101 | CEU101 | CEU101 |
| P2 | 0.5 mL | Deltoid (SC) | Placebo | Placebo | Placebo |
| III | T3 | 0.5 mL(1 x 106) | Deltoid (SC) | CEU101 | CEU101 | CEU101 |
| P3 | 0.5 mL | Deltoid (SC) | Placebo | Placebo | Placebo |
| IV | T4 | 0.5 mL(1 x 107) | Deltoid (SC) | CEU101 | CEU101 | CEU101 |
| P4 | 0.5 mL | Deltoid (SC) | Placebo | Placebo | Placebo |

## Study product formulation and preparation

#### **CEU101 (CEUVax, Inc.)**

CEU101 Vaccine is supplied as a sterile, clear solution in a 2 mL single-dose vial. The vaccine is provided at four different concentrations (1 x 104, 1 x 105, 1 x 106 or 1 x 107 IU per 0.5 mL) and is formulated with phosphate buffered saline, pH 7.2 ± 0.2, and a cryopreservative. Each vial contains approximately 0.7 mL of CEU101Vaccine. The product should be stored at –25° to –15°C (–13° to +5°F).

When preparing a dose in a syringe and administering the dose, consideration should be given to the volume of solution that may remain in the needle after the dose is administered. The clinic and pharmacy staff are encouraged to work together to administer the dose specified in the protocol.

Any unused portion of reconstituted vials and expired pre-filled syringes should be disposed of in accordance with institutional or pharmacy policy.

#### **Placebo**

The matching placebo is supplied as a sterile, clear solution in a 2 mL single-dose vial. The placebo is formulated with only phosphate buffered saline, pH 7.2 ± 0.2, and a cryopreservative. Each vial contains approximately 0.7 mL of solution. The product should be stored at –25° to –15°C (–13° to +5°F).

Any unused portion of reconstituted vials and expired pre-filled syringes should be disposed of in accordance with institutional or pharmacy policy.

## Study product administration

When preparing a dose in a syringe and administering the dose, consideration should be given to the volume of solution that may remain in the needle after the dose is administered. The pharmacy and clinic staff are encouraged to work together to administer the dose specified in the protocol. At sites where registered pharmacists are legally authorized to administer drug, the HVTU may choose to have the HVTU pharmacist administer the vaccinations.

## Study product acquisition

Study products will be provided by

At US HVTUs the pharmacist can obtain study products from the NIAID Clinical Research Products Management Center (CRPMC) by following the ordering procedures given in the section on Study Product Control inPharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

At non-US HVTUs the pharmacist can obtain study products from the NIAID Clinical Research Products Management Center (CRPMC). Once a non-US HVTU is registered for the study and all required documents have been received by DAIDS Pharmaceutical Affairs Branch, the Pharmacist can order product by following the procedures given in the**Error! Use the Home tab to apply Title Line 2 to the text that you want to appear here.** Study Specific Procedures (SSP)*.*

## Pharmacy records

The HVTU pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed. For US sites, all unused study products must be returned to the CRPMC after the study is completed or terminated. The procedures are included in the sections on Study Product Placebo and Drug Dispensing in Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. For non-US sites, specific instructions will be sent to the site after the study is completed or terminated.

The pharmacist of record is responsible for maintaining randomization codes and randomization confirmation notices for each participant in a secure manner.

# Clinical procedures

The schedule of clinical procedures is shown in Appendix G.

## Informed consent

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

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

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

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

### Screening consent form

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. Without a general screening consent, screening for a specific study cannot take place until the site is activated by HVTN Regulatory Affairs.

### 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,
* CRS’s institution and any applicable REs, and
* Elements of informed consent as described in Title 45, Code of Federal Regulations (CFR) Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, Good Clinical Practice: Consolidated Guidance 4.8.

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

The sample informed consent form includes instructions throughout the document for developing specific content.

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

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

### VISP registry consent form

Experimental HIV vaccines may induce antibody production to HIV antigens, producing reactive results on commercially available HIV test kits. This is called “vaccine-induced seropositivity” (VISP) (see Section 9.5.1). In order to provide post-study 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 post-study testing and counseling services to HIV vaccine recipients.

The VISP registry consent form describes the purpose of the VISP registry, the participant information to be included in the registry, confidentiality protections, and risks and benefits associated with inclusion in the registry. The VISP registry consent form is contained in **Error! Reference source not found.**.

The VISP Registry consent form will be presented to all participants. It is recommended to be presented no later than the last scheduled vaccination visit.

### 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. 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.

## 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 (record the complete generic name for all medications);
* Laboratory tests as defined in the inclusion and exclusion criteria, including:
*
* Administration of behavioral risk assessment questionnaire;
* Obtaining of volunteer demographics in compliance with the NIH Policy on Reporting Race and Ethnicity Data: Subjects in Clinical Research, Aug. 8, 2001 (available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html);
* Counseling on HIV testing and risk reduction, performed in compliance with the US Centers for Disease Control and Prevention (CDC)’s current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 9.5; and
* Discussion of pregnancy prevention. A pregnant or breastfeeding person may not be enrolled in this trial. Specific criteria and assessment of contraception and pregnancy status are described in study inclusion criteria. Discussion of pregnancy prevention includes advising a participant who was born female and who reports no current sexual activity that could lead to that participant becoming pregnant to have a plan to begin adequate birth control. This plan would be put to use if, during the study, the participant becomes sexually active in a way that could lead to that participant becoming pregnant.

### 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).

## Enrollment and vaccination visits

Enrollment is simultaneous with first vaccination. The time interval between randomization and enrollment should not exceed 4 working days. The HVTN CRS registers the participant by scheduling the day 0 visit (enrollment) via the Web-based randomization system, and requests the randomization assignment. Circumstances may require a participant’s enrollment visit to be changed. This may exceed the 4-day randomization time limit.

At all vaccination visits, the following procedures are performed before vaccination:

* Abbreviated physical examination, including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
* Assessment of baseline reactogenicity parameters;
* Assessment of concomitant medications (as described in Section 9.2);
* Assessment of any new or unresolved AEs/intercurrent illnesses; and
* Urine or serum pregnancy test (for participants who were born female).

Following completion of all procedures in the preceding list and results indicate that vaccination may proceed, vaccination is prepared and administered (see Sections **Error! Reference source not found.** and **Error! Reference source not found.**).

Administration of all injections during a vaccination visit must be accomplished within 1 calendar day.

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

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

* Risk reduction counseling (as described in Section 9.5);
* Pregnancy prevention assessment (as described in Section 9.2 and 9.6); and
* Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation).
* Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate; and
* Specimen collection (should be completed prior to vaccination)

## Follow-up visits

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

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

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

* Administration of the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
* Administration of a questionnaire that asks the participant about any HIV testing he or she may have received outside of the study. Participants will also be asked whether they believe they received the active vaccine or the control;
* HIV infection assessment including pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
* Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
* Abbreviated physical examination including weight, vital signs, and a symptom-directed evaluation by history and/or appropriate physical exam based on participant self-reported symptoms or complaints;
* Complete physical examination, including weight, vital signs, and clinical assessments of head, ears, eyes, nose, and throat; neck; lymph nodes; heart; chest; abdomen; extremities; neurological function; and skin;
* Specimen collection;
* Clinical laboratory tests including:
* CBC with differential and platelet count,
* Chemistry panel (see Section 9.2), and
* Urine dipstick (urinalysis if appropriate; see Section 9.7); and
* Urine or serum pregnancy test (for participants who were born female).

## HIV counseling and testing

HIV counseling will be performed in compliance with the CDC’s guidelines or other local guidelines for HIV counseling and referral. HIV testing will be performed in accordance with the current HVTN HIV testing algorithm following enrollment.

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

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

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

### 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 . 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 (as described in the HVTN Site Lab Reference Manual), 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).

## Contraception status

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

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

## 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.

## Assessments of reactogenicity

For all participants, baseline assessments are performed before and reactogenicity assessments are performed after each vaccination. All reactogenicity symptoms are followed until resolution and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification August 2009).

The reactogenicity assessment period is 3 full days following each vaccination per the assessment schedule shown in Table 9‑1. Participants are instructed to record symptoms using a postvaccination symptom log and to contact the site daily during the assessment period. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 3 to resolution. Participants are instructed to contact the clinic for events that arise during the period between vaccination and the next scheduled visit. In general, a participant who self-reports any postvaccination reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved.

Reactogenicity events are reported using CRFs that correspond to the time of assessment in Table 9‑1. Reactogenicity assessments include assessments of systemic and local symptoms, vaccine-related lesions, and lymph nodes. Events not listed on a CRF, or with an onset after the reactogenicity assessment period (day of vaccination and 3 full days after), or those meeting SAE/adverse events requiring expedited reporting to DAIDS criteria, are recorded on an adverse experience log form.

Table ‑ Schedule of reactogenicity assessments

|  |  |  |
| --- | --- | --- |
| Day | Time | Performed by |
| 0a | Baseline: before vaccination | HVTN CRS staff |
|  | Early: 25-60 minutes after vaccination | HVTN CRS staff |
|  | Between early assessment and 11:59pm day 0 | HVTN CRS staff or participant |
| 1 | Between 12:00am and 11:59pm day 1 | HVTN CRS staff or participant |
| 2 | Between 12:00am and 11:59pm day 2 | HVTN CRS staff or participant |
| 3b | Between 12:00am and 11:59pm day 3 | HVTN CRS staff or participant |

a Day of vaccination

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

### Assessment of systemic and local symptoms

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

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

### Assessment of injection site

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

All injection site reactions are monitored until resolution. Areas greater than 25 cm2 are followed daily; otherwise, the frequency of follow-up is based on clinician judgment.

### Assessment of lymph nodes

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

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

## Visit windows and missed visits

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

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

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

## 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, platelet count, and chemistry panel), pregnancy testing, social impact assessment, and HIV test.

## 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. In case of required termination, enrollment in an observational study should be offered to the participant. 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.

# Laboratory

## HVTN CRS laboratory procedures

The HVTN Site Lab Reference Manual provides further guidelines for operational issues concerning the clinical and processing laboratories. The manual includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

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

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

## 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.

## Primary immunogenicity timepoint

The primary immunogenicity timepoint in this study is at visit 7 (day 98) (ie, 2 weeks after the third vaccination visit). Endpoint assays for humoral and cellular responses are performed on participants at the primary immunogenicity timepoint and may be performed at baseline. Depending on the number of responders observed, assays for humoral and cellular responses may be performed on participants at other timepoints; the schedule is shown in Appendix E.

## Endpoint assays: cellular

### Flow cytometry

Flow cytometry will be used to examine vaccine-specific CD4+ and CD8+ T-cell responses following stimulation of PBMCs with synthetic HIV peptides that span the proteins encoded by the vaccine construct. ICS parameters will include cytokines such as IFN-γ, IL-2, and TNF-α, and may include other cytokines to identify T cells of specific functionality (such as Th2 and Th17). Markers of cytotoxic potential (Granzyme B, perforin and CD57) may also be included. Data will be reported as percentages of CD4+ or CD8+ T cells responding to a specific peptide pool. Additional cell surface markers, cytokines, or functional markers may also be analyzed.

### IFN-γ ELISpot

PBMCs will be stimulated overnight with synthetic peptide pools that span the proteins encoded by the vaccine constructs. This process will allow *ex vivo* HIV-specific T-cell data to be assessed by IFN-γ ELISpot as an immunogenicity endpoint. Data will be reported as the number of spot-forming cells (SFC) per 106 cells recognizing a specific peptide pool.

## Endpoint assays: humoral

### HIV-1 multiplex antibody assay

Total binding IgG (IgG1, IgG2, IgG3, IgG4) and IgA antibodies to (insert vaccine isolates here) will be assessed on plasma/serum samples from study participants taken at the primary immunogenicity timepoint and baseline. Specimens from other timepoints as well as other HIV antigens may also be assayed based on the results of the initial assay.

### Binding antibodies by ELISA

Binding antibodies to commercially available Env and Gag will be assessed at the HVTN Laboratory Program by ELISA using single serum dilutions (1/50 or 1/100) on samples from study participants taken at baseline and at the primary immunogenicity timepoint. Any of the timepoints that yield positive results in the initial ELISA may be subject to endpoint titration ELISA.

### Neutralizing antibody assay

HIV-1–specific neutralizing antibody assays will be performed on serum samples from all study participants taken at the primary immunogenicity timepoint. 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 timepoint. Tier 1 assays will test neutralization of HIV-1 strains represented in the highly neutralization-sensitive tier 1 viruses. The tier 2 assays will test neutralization of a panel of heterologous primary isolates. [14]

## Genotyping

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

## 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 time points. Please note that the Lab Assay Algorithm will be updated periodically to include new assays.

## 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.

## Other use of stored specimens

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

Other use of specimens is defined as studies not described in the protocol.

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

The protocol sample informed consent form is written so that the participant either explicitly allows or does not allow their samples to be used in other research when they sign the form. Participants who initially agree to other use of their samples may rescind their approval once they enter the study; such participants will remain in this study and their samples will only be used for the studies described in this protocol. If a participant decides against allowing other research using his or her samples, or at any time rescinds prior approval for such other use, the study site investigator or designee must notify HVTN Regulatory Affairs in writing. In either case, HVTN Regulatory Affairs directs the HVTN Lab Program not to use samples from these participants for such other uses.

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

## 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.

# Safety monitoring and safety review

## Safety monitoring and oversight

###  PSRT

The PSRT is composed of the following members:

* DAIDS medical officer representative,
* Protocol chair and cochair,
* Protocol Team leader,
* Core medical monitor, and
* SDMC Clinical Affairs safety associate.

The clinician members of HVTN 999 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, project manager, vaccine developer representative, clinical trial manager, and others may also be included in HVTN 999 PSRT meetings.

### 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 PDC: Delete through the end of the sentence if study does not have an Annual Health Contacts period: during the main study, as defined in Section 3 (for safety reviews during the annual health contacts period, please see Section 9.5). The reviews consist of evaluation of cumulative reactogenicity events, AE, laboratory safety data, and individual reports of adverse events requiring expedited reporting to DAIDS. To increase the sensitivity for detecting potential safety problems, the SMB will review safety data aggregated across multiple protocols that use the same or similar vaccine candidates. The SMB conducts additional special reviews at the request of the PSRT.

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

### 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 PSRT and HVTN SMB (see Section 11.1.2);
* Daily monitoring of clinical data for events that meet the safety pause and PSRT AE review criteria (see Section 11.4);
* Notifying HVTN CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.4);
* Querying HVTN CRSs for additional information regarding reported clinical data; and
* Providing support to the PSRT.

## Safety reporting

### Submission of safety forms to SDMC

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

### AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational study product/procedure(s), whether or not related to the investigational study product/procedure(s). All AEs are graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), Version 1.0, December 2004 (Clarification dated August 2009), available on the RSC website at http://rsc.tech-res.com/safetyandpharmacovigilance/, except that unintentional weight loss of less than 10% loss in body weight from baseline is not required to be reported as an adverse event.

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

Sites are expected to notify SDMC Clinical Affairs staff of any serious safety concern requiring their attention (see Table 11‑1). Telephone numbers and email addresses are listed in the Key Resource Guide of the Study Specific Procedures. Concerns requiring immediate attention should be communicated by calling the SDMC Clinical Affairs safety phone.

In the case of email notification, SDMC Clinical Affairs staff will reply during working hours (US Pacific Time) to confirm that the email has been received and reviewed. If email service is not available, the HVTN CRS should notify SDMC Clinical Affairs 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.

### Expedited reporting of adverse events to DAIDS

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

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

Sites where DAERS has not been implemented will submit expedited AE reports by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: http://rsc.tech-res.com/safetyandpharmacovigilance/. For questions about expedited AE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

The study products for which expedited reporting are required are:

* CEU101
* In addition to the expedited Reporting Category identified above, other AEs that must be reported in an expedited manner are: all cancers, all myopericarditis events, all hepatic failures, all autoimmune diseases.

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

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

The NIAID/DAIDS will report all unexpected SAEs related to the study products observed in this clinical trial to the FDA in accordance with 21 CFR 312.32 (IND Safety Reports). However, because safety is a primary study endpoint, the Sponsor Medical Officer will not be unblinded to study treatment assignment when there is an assessment of relatedness of the SAE with the study product(s); and the safety report will be sent to the FDA based on the blinded attribution assessment.

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

## Safety reviews

### Initial safety evaluation

Enrollment across all participating HVTN CRSs will be restricted to a maximum of 1 participant per day and restricted to US sites until 5 participants have been enrolled in each group. The PSRT will review the cumulative safety data including at minimum local and systemic reactogenicity data reported for the first 72 hours postvaccination on each of these 5 participants, and will determine whether it is safe to proceed with full enrollment in that group. If enrollment proceeds in the US following the safety review, then enrollment in these groups may also be initiated at sites outside the US.

### Safety considerations for dose escalation

In addition to monitoring participant safety throughout the study period, the 999 PSRT will review cumulative safety data available on all participants in each group up to and including the 2-week visit after the second vaccination to determine whether dose escalation may occur. The PSRT may consult with the HVTN SMB on an ad hoc basis for these evaluations.

## 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 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 999 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 ‑ AE notification and safety pause/AE review rules

|  |  |  |  |
| --- | --- | --- | --- |
| Event and relationship to study products | Severity | HVTN CRS action | SDMC action |
| SAE, related | Grade 5 or Grade 4 | Phone immediately, email and fax forms immediatelya | Immediate pause |
| SAE, not related | Grade 5 | Phone immediately, email and fax forms immediately | Immediate HVTN 999 PSRT notification |
| SAE, related | Grade 3 | Email and fax forms immediately | Prompt HVTN 999 PSRT AE review to consider pause |
| AEb, related | Grade 4 or 3 | Email and fax forms immediately | Prompt HVTN 999 PSRT AE review to consider pause |

 Phone numbers and email addresses are listed in Study Specific Procedures, Key Resource Guide.

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

For all safety pauses, the SDMC Clinical Affairs staff notifies the HVTN 999 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, the SDMC Clinical Affairs staff also notifies the HVTN SMB.

Once a trial is paused, the PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of vaccination is appropriate, consulting the SMB if necessary. SDMC Clinical Affairs staff 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 PSRT assessment, DAIDS RAB notifies the FDA as needed.

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

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

In addition, all other AEs are reviewed routinely by the PSRT (see Section 11.5.2).

## 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.

### Daily review

Blinded daily safety reviews are routinely conducted by the SDMC Clinical Affairs staff for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt PSRT AE review criteria.

### Weekly review

During the injection phase of the trial, the SDMC Clinical Affairs staff and the PSRT review clinical safety reports on a weekly basis and conduct 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 PSRT. The SDMC Clinical Affairs staff 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.

## Study termination

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

# Protocol conduct

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

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

Any policies or procedures that vary from DAIDS and HVTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 999 *Study Specific Procedures.*

## 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.

## Emergency communication with study participants

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

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

# 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 999 are described below.

Protocol history and modifications

Date: 15 October 2013

Protocol version:1.0

# Document references (other than literature citations)

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

* Assessment of Understanding. Accessible through the HVTN protocol-specific website.
* Current CDC Guidelines. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf.
* Division of AIDS (DAIDS) Clinical Research Policies and Standard Procedures Documents. Available at http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/
* Division of AIDS Protocol Registration Manual. Available at http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/prmanual.pdf
* Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Version 1.0, December 2004. (Clarification dated August 2009) Available at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx
* The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at http://rsc.tech-res.com/safetyandpharmacovigilance/manualforexpeditedreporting.aspx
* HVTN Certificate of Confidentiality. Accessible through the HVTN website.
* HVTN 999 Special Instructions. Accessible through the HVTN protocol-specific website.
* Study Specific Procedures. Accessible through the HVTN protocol-specific website.
* HVTN Site Lab Reference Manual. Accessible through the HVTN website.
* HVTN Manual of Operations. Accessible through the HVTN website.
* Dangerous Goods Regulations (updated annually), International Air Transport Association. Available for purchase at <http://www.iata.org/ps/publications/dgr/Pages/index.aspx>.
* Lab assay algorithm
* HVTN algorithm for diagnosis of HIV infections. Part of the HVTN Site Lab Reference Manual (see above).
* International Conference on Harmonisation (ICH) E6 (R1), Guideline for Good Clinical Practice: Section 4.8, Informed consent of trial subjects. Available at http://www.ich.org/fileadmin/Public\_Web\_Site/ICH\_Products/Guidelines/Efficacy/E6\_R1/Step4/E6\_R1\_\_Guideline.pdf
* Participants’ Bill of Rights and Responsibilities. Accessible through the HVTN website.
* NIH Guidelines for Research Involving Recombinant DNA Molecules. Available at http://oba.od.nih.gov/rdna/nih\_guidelines\_oba.html.
* 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://phacs.nichdclinicalstudies.org/publicDocs/DAIDS\_SourceDocPolicy.pdf
* Title 21, Code of Federal Regulations, Part 50. Available at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=2e2429c70115b7df5635f222901ae8f7&rgn=div5&view=text&node=21:1.0.1.1.19&idno=21
* Title 45, Code of Federal Regulations, Part 46. Available at http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&sid=2e2429c70115b7df5635f222901ae8f7&rgn=div5&view=text&node=45:1.0.1.1.25&idno=45

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

# Acronyms and abbreviations

Ab antibody

Ad adenovirus

AE adverse event

ALT alanine aminotransferase

ANOVA analysis of variance

ART antiretroviral therapy

AST aspartate aminotransferase

AVEG AIDS Vaccine Evaluation Group

β-HCG beta human chorionic gonadotropin

BMI body mass index

CAB Community Advisory Board

CBC complete blood count

CDC US Centers for Disease Control and Prevention

CFR Code of Federal Regulations

CIOMS Council for International Organizations of Medical Sciences

CI confidence intervals

CRF case report form

CRPMC NIAID Clinical Research Products Management Center

CRS\* clinical research site

CTL cytotoxic T lymphocyte

DAERS DAIDS Adverse Event Reporting System

DAIDS Division of AIDS (US NIH)

DHHS US Department of Health and Human Services

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

ELISpot enzyme-linked immunospot

FDA US Food and Drug Administration

FHCRC Fred Hutchinson Cancer Research Center

FPR false positive rate

GCP Good Clinical Practice

GEE generalized estimating equation

HAART highly active antiretroviral therapy

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 Conference on Harmonisation

ICS intracellular cytokine staining

IFN-γ interferon gamma

IND Investigational New Drug

IRB Institutional Review Board

IUD intrauterine device

LTFU loss to follow-up

MAR missing at random

MCAR missing completely at random

MMR measles, mumps, and rubella

nAb neutralizing antibody

NHP nonhuman primate

NIAID National Institute of Allergy and Infectious Diseases (US NIH)

NICD National Institute for Communicable Diseases (Johannesburg, South Africa)

NIH US National Institutes of Health

OBA NIH Office of Biotechnology Activities

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

PSRT Protocol Safety Review Team

PTE potential T-cell epitope

RAB DAIDS Regulatory Affairs Branch

RAC NIH Recombinant DNA Advisory Committee

RE regulatory entity

RSC DAIDS Regulatory Support Center

SAE serious adverse event

SCHARP Statistical Center for HIV/AIDS Research and Prevention

SDMC statistical and data management center

SFC spot-forming cell

SFU spot-forming unit

SIV simian immunodeficiency virus

SMB Safety Monitoring Board

SPT DAIDS Safety and Pharmacovigilance Team

TB tuberculosis

UW-VSL University of Washington Virology Specialty Laboratory

VISP Vaccine induced seropositivity

VRC Vaccine Research Center (NIAID)

\* CRSs were formerly referred to as HIV Vaccine Trial Units (HVTUs). Conversion to use of the term CRS is in process, and some HVTN documents may still refer to HVTUs.

# Literature cited

 1. UNAIDS. Ethical considerations in biomedical HIV prevention trials. 2007.

 2. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research. 1979.

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

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

 5. Berger RL, Boos DD. P Values Maximized Over a Confidence Set for the Nuisance Parameter. Journal of the American Statistical Association 1994;89:1012-6.

 6. Lachenbruch PA. Comparisons of two-part models with competitors. Stat Med 2001;20:1215-34.

 7. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two success and two failures. American Statistician 2000;54:280-8.

 8. Bechhofer RE, Santner TJ, Goldsman DM. Design and analysis of experiments for statistical selection, screening, and multiple comparisons. New York: John Wiley & Sons, 1995.

 9. Hudgens MG. Estimating cumulative probabilities from incomplete longitudinal binary responses with application to HIV vaccine trials. Statistics in Medicine 2003;22:463-79.

 10. Hughes JP. Mixed effects models with censored data with application to HIV RNA levels. Biometrics 1999;55:625-9.

 11. Rotnitzky A, Robins J. Analysis of semi-parametric regression models with non-ignorable non-response. Stat Med 1997;16:81-102.

 12. Huang Y GPMDSS. Simultaneous evaluation of the magnitude and breadth of a left- and right-censored multivariate response, with application to HIV vaccine development. Statistics in Biopharmaceutical Research 2009;1:81-91.

 13. Liu W. On sample size determination of Dunnett's procedure for comparing several treatments with a control. Journal of Statistical Planning and Inference 1997;62:255-61.

 14. Seaman M, Janes H, Hawkins N, randpre L, Devoy C, Giri A, Coffey R, Harris L, Wood B, Daniels M, Bhattacharya T, Lapedes A, Polonis V, McCutchan F, Gilbert P, Self S, Korber B, Montefiori D, Mascola J. Tiered Categorization of a Diverse Panel of HIV-1 Env Pseudoviruses for Assessment of Neutralizing Antibodies. J Virol 2010;84:1439-52.

15. Bloch C. Epidemiological HIV/AIDS situation in Argentina. Actualizaciones en SIDA 2001;9 Suppl:15-24.

16. Sanchez JL, Whittington WLH, Zuckerman RA, Ashley RL, Lama JR, Galvan R. Bacterial STDs and HSV-2 acquisition among MSM HIV seroconverters in Peru. Conf HIV Pathog Treatm, Buenos Aires, Argentina, 7-8-2001.

17. Lama JR, Goicochea LP, Chion M, et al. [Comportamiento sexual y factores de riesgo para ETS e infeccion VIH entre hombres que tienen sexo con otros hombres de Lima, Peru]. Pan-American Conference on AIDS, Lima, Peru, 12-3-1997.

18. Tabet S, Sanchez J, Lama J, et al. HIV, syphilis and heterosexual bridging among Peruvian men who have sex with men. AIDS 2002;16:1271-7.

19. Schechter M, Strathdee SA, Martindale SL, et al. Evidence of elevated HIV incidence and relapse to unsafe sex among young men having sex with men (MSM) in Vancover Canada. Int Conf AIDS, 6-28-1998.

20. Fauci AS. The AIDS epidemic--considerations for the 21st century. N Engl J Med 1999;341:1046-50.

21. Varmus H, Nathanson N. Science and the control of AIDS. Science 1998;280:1815.

22. Bechhofer RE, Santner TJ, Goldsman DM. Design and analysis of experiments for statistical selection, screening, and multiple comparisons. New York: John Wiley & Sons, 1995.

23. Hudgens MG. Estimating cumulative probabilities from incomplete longitudinal binary responses with application to HIV vaccine trials. Statistics in Medicine 2003;22:463-79.

24. Lachenbruch PA. Comparisons of two-part models with competitors. Stat Med 2001;20:1215-34.

1. Sample informed consent form

Title: A Phase I Safety and Immunogenicity Trial of an Alphavirus Replicon HIV Subtype C *Gag* Vaccine (CEU101, CEUVax, Inc.) in Healthy HIV-1 Uninfected Adult Volunteers

HVTN protocol number:

Site:

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 are doing a study to test an HIV vaccine. HIV is the virus that causes AIDS.

About 96 people will take part in this study at sites in the United States and South Africa. The researcher in charge of this study at this clinic is . The US

National Institutes of Health (NIH) is paying for the study.

* 1. We are doing this study to answer several questions.
* Is the study vaccine safe to give to people?
* Are people able to take the study vaccine without becoming too uncomfortable?
* How do people’s immune systems respond to the study vaccine? (Your immune system protects you from disease.)
* Does the vaccine have different effects at different doses?
	1. The study cannot give you HIV.

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

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

Sites: Any change to the language in this section requires approval from HVTN Regulatory Affairs.

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 another study, some men who got the vaccine had a *higher* risk of getting HIV than men who did not get the vaccine. Only a few women in that study got HIV. We can’t tell if the vaccine affected their risk.

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

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

* 1. This study vaccine is experimental.

The study vaccine is called CEU101. From here on, we will call it CEU101 or the study vaccine. It is an experimental HIV vaccine. That means we do not know whether the vaccine will be safe to use in people, or whether it will work to prevent HIV infection. This vaccine is used only in research studies.

The vaccine was developed by CEUVAX, Inc. The vaccine contains a part of the HIV virus that makes one HIV protein. The vaccine also contains parts of another virus, called Cascadian ursus virus (CUV) virus, which acts as a carrier, to allow the vaccine to enter cells. Only selected parts of a weakened strain of CUV virus are used in the CEU101 vaccine.

Infection with a related virus - whole, unmodified CUV virus - can cause fever and inflammation of the nervous system in humans and animals and death in about 1% of humans that become infected with it. However, the CEU101 vaccine is not made from unmodified CUV virus. Instead, only selected parts of a weakened strain of CUV virus are used in the CEU101 vaccine.

A similar weakened strain of CUV has been used as a live virus vaccine in people for decades. In addition, the CEU101 vaccine is designed so it cannot make any live viruses, and it is tested after being made to show that no live viruses are present. There is a remote possibility that the vaccine may contain very small numbers of live carrier weakened CUV virus that were not detected in the safety tests, in which case you might become infected by the weakened CUV virus. Infection with weakened vaccine CUV virus could cause you to develop a fever, headache or general discomfort. After the vaccine is injected and enters the cells in your arm, part of the vaccine will replicate within the cells and will make the HIV protein, which we hope will allow your immune system to make antibodies and immune cells against the HIV protein.

CEU101 is a novel vaccine that has never been given to humans before the current study, so there is no information available about the safety of this vaccine in people. The vaccine was safe when tested in animals, but results in animals do not always predict results in people.

General risks of vaccines:

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

All vaccines can cause fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired. Most people can still do their planned activities after getting a vaccine. Rarely, people experience side effects that limit their normal activities or make them go to the doctor.

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

Joining the study

* 1. 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 receive a study product. Also during the study, you should not donate blood or tissue.

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

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

* 1. If you decide 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 ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV. If you were born female, we will test you for pregnancy.

We will review the screening results with you, and offer you counseling and referral if you need medical care. We will not pay for this medical care. The screening results may show you are not eligible to join the study, even if you want to.

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

Site: List approved birth control methods here if you do not want to hand out the separate Approved Birth Control Methods sheet.

You should not become pregnant during the study because we do not know how the study vaccine could affect the developing baby. You must agree to use effective birth control from 1 month before your first injection until the end of the study. We will talk to you about effective birth control methods. They are listed on a handout that we will give to you. *Site: Delete the preceding sentences if you include the birth control sheet in this consent form.* If you join the study, we will test you for pregnancy at some visits, including before each study injection.

Being in the study

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

* 1. You will come to the clinic for scheduled visits about 9 times over one year.

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

Visits can last from to hours.

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

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

* 1. We will give you for each study visit you complete.

This amount is to cover the costs of

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

US sites only:

Payments you receive for being in the study may be taxable. This happens if we pay you more than $600 between January 1 and December 31 of the same year. The clinic staff 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.

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

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

Site: Modify the randomization metaphor in the below paragraph as appropriate to your local culture.

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

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

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

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

You will be in one of 4 groups. You will get 3 injections during the study by injection into the upper arm.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | US | South Africa |  | Vaccination schedule in months (days) |
| Study arm | Number | Number | Dose | 0 (0) | 1 (28) | 3 (84) |
|  |  |  |  |  |  |  |
| Group 1 | 10 | 10 | Low dose | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |
| Group 2 | 10 | 10 | Medium-low dose | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |
| Group 3 | 10 | 10 | Medium-high dose | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |
| Group 4 | 10 | 10 | High dose | vaccine | vaccine | vaccine |
|  | 2 | 2 |  | placebo | placebo | placebo |
|  |  |  |  |  |  |  |
| Total | 48 (40 vaccine/8 placebo) | 48 (40 vaccine/8 placebo) |  |  |  |  |

You will have to wait in the clinic for about a half hour after each injection to see if there are any problems. Then for that night and for three more days, you will need to write down how you are feeling and if you have any symptoms. Contact the clinic staff if you have any issues or concerns after receiving an injection. If you have a problem, we will continue to check on you until it goes away.

* 1. 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;
* Perform physical exams;
* Take blood and urine samples;
* Do pregnancy tests if you were born female;
* Ask questions about your health, including medications you may be taking;
* Ask questions about any personal problems or benefits you may have from being in the study; and

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 25 mL and 160 mL (2 tablespoons to 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: Paste table of procedures in this section or distribute it as a separate sheet if it is helpful to your study participants.

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. We will also offer you counseling and referral for needed care.

13. We will counsel you on avoiding HIV infection.

We will ask you personal questions about your HIV risk factors such as sexual behavior and drug use. We will talk with you about ways to keep your risk of getting HIV low. Some topics we may discuss include:

• What you think may cause risky behavior for you.

• Methods to avoid getting HIV.

These may include not having sex, using condoms, or behavior changes, such as cutting down on alcohol. We will talk with you about which methods of HIV prevention may be right for you.

* 1. We will test your samples for this study.

We will send your samples (without your name) to a lab to see how your immune system responds to the study products. This may include limited genetic testing. Your genes are passed to you from your birth parents. They affect how you look and how your body works. Limited genetic testing involves only some of your genes, not all of your genes (your genome). The researchers will not look at all of your genes, only the genes related to the immune system and diseases. These tests are for research purposes only. The lab will not give the results to you or this clinic, and the results will not become part of your study record.

Site: Delete Section 14 if using separate Other Use of Specimen consent

* 1. When we take samples from you for this study, we take extra samples in case we have to repeat tests. When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies. We will call these “extra samples.”

This section gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

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

*Where are the samples stored?* Extra samples are stored in a secure central place called a repository.[Site: insert specific information if your regulatory authority requires it.]The central repositories for the HVTN are located in the United States and South Africa.

PDC: Add text above informing participants of any international shipping of their samples.

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

*Will I be paid for the use of my samples?* No. Also, a researcher may make a new scientific discovery or product based on the use of your samples. If this happens, there is no plan to share any money with you. The researcher is not likely to ever know who you are.

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

*Will the HVTN sell my samples and information?* No, but the HVTN may share your samples with other researchers.

*How do other researchers get my samples and information?* When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: insert review by your institution’s IRB/EC, if applicable.] IRBs/ECs protect the rights and well-being of people in research. The HVTN keeps track of your decision about how your samples and information can be used.

*What information is shared with other researchers?* We will not share any information that would make it easy for anyone to identify you. 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.

*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 will need to ask your permission for other types of research not described in this informed consent. Tell us below if you want researchers to contact you about using your extra samples for studies that are not mentioned in this consent.

The studies will probably include genetic testing. Your genes are passed to you from your birth parents. Genes are the basic “instruction book” for the cells that make up our bodies. The differences in people’s genes can help explain why some people get a disease while others do not.

Researchers will only look at the genes that may be related to the immune system and diseases. They will not look at all of your genes (your genome). We call this “limited genetic testing.” For example, researchers may look at genes that affect how you fight infection. If you agree to have your samples and information used for other studies, you are also agreeing to this kind of limited genetic testing.

*What are the risks of limited genetic testing?* The genetic testing could show you may be at risk for certain diseases or that you are or are not related to someone. 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 extra samples.

Remember:

* The results are not given to you, this clinic, or your doctor.
* The results are not linked to your name.
* The researchers who use your samples and information have agreed never to find out who you are.
* The results are not a part of your medical record.

Someone could try to find out who you are. For this to happen, that person would have to get into another database that links your study information and your name. The risk of this is very small.

[U.S. Sites, include the following paragraph]

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

*Who will have access to my information in studies using my extra samples?* Some people will be able to see the research records from any new study that uses your extra samples and information. Remember that your name will not be part of the information.

People who may see your information are:

* Government agencies that fund or monitor the research using your samples or information
* The researcher’s Institutional Review Board or Ethics Committee
* The people who work with the researcher

The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally..

**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 .

If you think you may have been harmed because of studies using your samples or information, contact .

If you have questions about your rights as a research participant, contact

* 1. We will do our best to protect your private information.

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

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

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

These groups include:

* The US National Institutes of Health and its study monitors,
* The US Food and Drug Administration,
* ,
* ,
* CEUVAX, Inc. and people who work for them,
* The HVTN and people who work for them,
* The HVTN Safety Monitoring Board or the NIAID Data and 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.).

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

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

Delete the highlighted part below if using a separate *Other Use of Specimen* consent:

Researchers who use your stored samples and limited information for other research will also do their best to protect your private information. The samples and limited information they receive will be labeled with a code number. They will not have your name or any personal information. Any reviewers of those studies will take steps to keep your records private.

The results of this study, (Delete the highlighted part if using a separate *Other Use of Specimen* consent) and other studies that use the samples or information you agree to donate, 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 personal information.

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

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

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. 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.

* 1. 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 additional injections.

This may happen if:

* you do not follow instructions,
* the researcher thinks that staying in the study might harm you,
* you get HIV,
* you enroll in a different research study where you receive 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.

* 1. If you become pregnant during the study, we will continue with some procedures but not injections.

We will do this for as long as it is safe for you and your developing baby.

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.

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

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

Other Risks

* 1. 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, muscle damage, and (rarely) infection where the needle was inserted. 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 study vaccine may cause you to test positive on some types of HIV tests. This is called vaccine-induced seropositivity (VISP). VISP means that after you get the study vaccine, a routine HIV test done outside this clinic may say you have HIV, even if you don’t. For this reason, you should plan to get HIV tests only at this clinic during the study. Our tests can tell the difference between true HIV infection and a positive result that is caused by the study vaccine.

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

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

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

Site: Modify the preceding paragraph if applicable.

Site: Delete the following paragraph if local HIV testing of newborns is done via nucleic acid test.

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. But, the antibodies from the mother go away over time. If needed, we will arrange for the baby to have a test that can tell the difference between true HIV infection and a VISP result. We can do 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.

Unknown risks:

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

We do not know if getting this study vaccine will affect how you respond to any future approved HIV vaccine. It could be that a future HIV vaccine may not work as well for you because you got the study vaccine. Currently, no HIV vaccine has been approved for use.

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

Benefits

* 1. The study may not benefit you.

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

This study may help in the search for a vaccine to prevent HIV. However, if the study later become approved and sold, there are no plans to share any money with you. Delete the following sentence if using a separate Other Use of Specimen consent: You will also not receive any money if you decide to donate your extra samples and limited information for other research, even if this research leads to a new product or discovery.

Your rights and responsibilities

* 1. 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

* 1. 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

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

Your health is important to us. We will help you get the medical care you need.

If someone gets sick or injured in an HVTN study, the HVTN decides whether the injury is probably related to the study product and/or procedures. If the HVTN decides it was more likely due to the study product or procedures than any other cause, then the HVTN and/or CEUVAX, Inc. will use their funds to pay for treatment. If the HVTN decides otherwise, then you and your health insurance (Sites: insert locale- appropriate medical insurance language in the preceding sentence) would be responsible for treatment costs.

You may disagree with the decision the HVTN makes about your injuries. At your request the HVTN will ask experts who are not connected with the HVTN to review its decision.

In this study, CEUVAX, Inc. will pay the cost of medical expenses that arise from injuries caused by the study products.

For injuries caused by study procedures, the HVTN has limited funds to cover the cost of medical treatment.

No matter what, you still have the right to use the court system to address payment for your injuries if you are not satisfied.

Some injuries are not physical. For example, someone might be harmed psychologically or emotionally by being in an HIV vaccine study. Or they might lose wages from injuries because they could not go to work. No funds have been set aside to pay for nonphysical injuries, even if they are related to participation in the study.

Questions

* 1. 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 .

If you have any symptoms that you think may be related to this study, contact .

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 .

If you want to leave this study, contact .

 Your permissions and signature

Site: Delete this section if using a separate consent for Other Use of Specimens

* 1. In Section 14 of this form, we told you about possible other uses of your extra samples and limited information, outside this study. Please write your initials or make your mark in the box next to the option you choose.

|  |  |
| --- | --- |
|  | I agree to allow my extra samples combined with limited information for other studies related to HIV, the immune system, and other diseases. This may include limited genetic testing.  |
| **OR** |  |
|  | I do not agree to allow my extra samples and information to be used in other studies |
|  |  |
|  | I agree to be contacted in the future for other types of research not described in this informed consent. |

* 1. 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 consentdiscussion (print) |  | Clinic staff signature |  | Date |  | Time |

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| Witness’s name (print) |  | Witness’s signature  |  | Date |  | Time |

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

1. Approved birth control methods (for sample informed consent form)

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

If you were born female and are sexually active in a way that could lead you to get pregnant, you must agree to use effective birth control, from one month before your first injection until the end of the study.

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

* Birth control drugs that prevent pregnancy—given by pills, shots, patches, vaginal rings, or inserts under the skin;
* Male or female condoms, with or without a cream or gel that kills sperm;
* Diaphragm or cervical cap with a cream or gel that kills sperm;
* Intrauterine device (IUD); or
* Any other contraceptive method approved by the researchers.

You do not have to use birth control if:

* You are only having sex with a partner or partners who have had a vasectomy. (We will ask you some questions to confirm that the vasectomy was successful.);
* You have reached menopause, with no menstrual periods for one year;
* You have had a hysterectomy (your uterus removed);
* You have had your ovaries removed;
* You have a tubal ligation (your “tubes tied”) or confirmed successful placement of a product that blocks the fallopian tubes;
* You are having sex only with a female partner or partners;
* You only have oral sex; or,
* You are sexually abstinent (no sex at all).

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

1. Sample consent form for use of samples and information in other studies

Title: A Phase I Safety and Immunogenicity Trial of an Alphavirus Replicon HIV Subtype C *Gag* Vaccine (CEU101, CEUVax, Inc.) in Healthy HIV-1 Uninfected Adult Volunteers

HVTN protocol number:

Site:

When samples are no longer needed for this study, the HVTN wants to keep them for use in other studies. We will call these “extra samples.”

This form gives you information so you can decide if you want your extra samples and information used in other studies. You will mark your decision at the end of the form. If you have any questions, please ask.

* 1. Do I have to agree?

No. You are free to say yes or no, or to change your mind after you sign this form. Your decision will not affect your being in this study or have any negative consequences here.

* 1. Where are the samples stored?

Extra samples are stored in a secure central place called a repository. [Site: insert specific information if your regulatory authority requires it.]The central repositories for the HVTN are located in the United States and South Africa.

* 1. How long will the samples be stored?

There is no limit on how long your extra samples will be stored. [Site: insert limits if your regulatory authority imposes them.]

* 1. 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.

* 1. 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 needed for your medical care. They are not part of your medical record. The studies are only being done for research purposes.

* 1. Will the HVTN sell my samples and information?

No, but the HVTN may share your samples with other researchers.

* 1. How do other researchers get my samples and information?

When a researcher wants to use your samples and/or information, their research plan must be approved by the HVTN. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review their plan. [Site: insert review by your institution’s IRB/EC, if applicable.]IRBs/ECs protect the rights and well-being of people in research. The HVTN keeps track of your decision about how your samples and information can be used.

* 1. What information is shared with other researchers?

We will not share any information that would make it easy for anyone to identify you. 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.

* 1. How is my privacy protected?

Your samples are labeled with a code instead of your name. We will not tell the researchers who you are.

* 1. 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 will need to ask your permission for other types of research not described in this informed consent. Tell us below if you want researchers to contact you about using your extra samples for studies that are not mentioned in this consent.

The studies will probably include genetic testing. Your genes are passed to you from your birth parents. Genes are the basic “instruction book” for the cells that make up our bodies. The differences in people’s genes can help explain why some people get a disease while others do not.

Researchers will only look at the genes that may be related to the immune system and diseases. They will not look at all of your genes (your genome). We call this “limited genetic testing”. For example, researchers may look at genes that affect how you fight infection. If you agree to have your samples and information used for other studies, you are also agreeing to this kind of limited genetic testing.

* 1. What are the risks of limited genetic testing?

The genetic testing could show you may be at risk for certain diseases or that you are or are not related to someone. 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 extra samples.

Remember:

* The results are not given to you, this clinic, or your doctor.
* The results are not linked to your name.
* The researchers who use your samples and information have agreed never to find out who you are.
* The results are not a part of your medical record.

Someone could try to find out who you are. For this to happen, that person would have to get into another database that links your study information and your name. The risk of this is very small.

[U.S. Sites, include the following paragraph]

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

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

Some people will be able to see the research records from any new study that uses your extra samples and information. Remember that your name will not be part of the information.

People who may see your information are:

* Government agencies that fund or monitor the research using your samples or information
* The researcher’s Institutional Review Board or Ethics Committee
* The people who work with the researcher

All reviewers will take steps to keep your records private.

The results of any new studies that use your extra samples or information may be published. No publication will use your name or identify you personally.

Questions

* 1. 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 .

If you think you may have been harmed because of studies using your samples or information, contact .

If you have questions about your rights as a research participant, contact .

* 1. Please write your initials or make your mark in the box next to the option you choose.

|  |  |
| --- | --- |
|  | I agree to 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 limited genetic testing.  |
| **OR** |  |
|  | I do not agree to allow my extra samples and information to be used in other studies. |
|  |  |
|  | I agree to be contacted in the future for other types of research not described in this informed consent. |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| Participant’s name (print) |  | Participant’s signature or mark |  | Date |  | Time |
|  |  |  |  |  |  |  |
| Clinic staff conducting consentdiscussion (print) |  | Clinic staff signature |  | Date |  | Time |

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

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |
| Witness’s name (print) |  | Witness’s signature  |  | Date |  | Time |

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

1. Table of procedures (for sample informed consent form)

|  |  |
| --- | --- |
|  | Time after 1st injection visit (in months) |
| Procedure | Screening visit(s) | 1st injection visit | ½ | 1 | 2  | 2½ | 5 | 8 |
| Injection |  | √ |  | √ | √ |  |  |  |
| Medical history | √ |  |  |  |  |  |  |  |
| Complete physical | √ |  |  |  |  |  |  | √ |
| Brief physical |  | √ | √ | √ | √ | √ | √ |  |
| Urine test | √ |  | √ |  |  | √ |  | √? |
| Blood drawn | √ | √ | √ |  | √ | √ | √ | √ |
| Pregnancy (women) | √ | √ |  | √ | √ |  |  | √ |
| HIV testing/counseling | √ |  |  | √ |  | √ | √ | √ |
| Interview/questionnaire | √ | √ | √ | √ | √ | √ | √ | √ |
| Risk reduction counseling | √ | √ | √ | √ | √ | √ | √ | √ |

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. Laboratory procedures

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **Visit** | **01** | **02** | **03** | **04** | **05** | **06** | **07** | **08** | **09** |
|  |  |  |  | **Day** | **Prior to VAC1** | **D0** | **D14** | **D28** | **D42** | **D84** | **D98** | **D168** | **364** |
|  |  |  |  | **Month** |  | **M0** |  | **M1** |  | **M3** |  | **M6** | **M12** |
|  |  |  |  |  | **Screening** | **VAC1** |  | **VAC2** |  | **VAC3** |  |  |  |
| **LABORATORY ASSAYS** | **SHIPPING LOCATION[[6]](#footnote-1),[[7]](#footnote-2)** | **ASSAY LOCATION** | **TUBE TYPE** | **VOLUME REQUIRED FOR ASSAY (mL)** |
| **Humoral** | HIV Screening ELISA, Western Blot as indicated[[8]](#footnote-3),[[9]](#footnote-4) | CL-Richmond | CL-Richmond  | SST | 5 |  |  |  |  |  | 5 | 5 | 5[[10]](#footnote-5) |
|  | HIV-1 Gag ELISA | CSR | CL-Duke | SST |  | 7 |  |  | 7 |  | 7 | 7 | 7 |
|  | Anti-CUV antibodies | CSR | CEUVax | SST | 7 |  |  |  | 7 |  | 7 | 7 | 7 |
| **Viral** | HIV RNA PCR[[11]](#footnote-6) | CL-Richmond | CL-Richmond | PPT |  | 5 |  |  | 5 |  | 5 | 5 | 5 |
|  | HIV DNA PCRf | CL-Richmond | CL-Richmond | ACD |  | 7 |  |  | 7 |  | 7 | 7 | 7 |
|  | CUV Viral Culture[[12]](#footnote-7) | CEUVax[[13]](#footnote-8) | CEUVax | SST |  |  | 7g |  | 7g |  | 7g |  |  |
| **Cellular** | IFN-γ ELISPOT | CSR | CL-Duke | Na Hep |  | 40 |  |  | 40 |  | 40 | 40 | 40 |
|  | EBV transformation / HLA typing | CL-Duke | CL-Duke | ACD | 20 | [20][[14]](#footnote-9) |  |  |  |  |  |  |  |
|  | CTL | CL-Duke | CL-Duke | Na Hep |  | 30[[15]](#footnote-10) |  |  | 30 |  | 30 | 30 | 30 |
|  | FACS Intracellular Cytokine Staining (ICS) | CSR | CL-Duke | Na Hep |  | 20 |  |  | 20 |  | 20 | 20 | 20 |
|  | LPA | CSR | CL-Duke | Na Hep |  | 10 |  |  | 10 |  | 10 | 10 | 10 |
| **SPECIMEN STORAGE** | **SHIPPING LOCATION** | **STORAGE LOCATION** | **TUBE TYPE** | **VOLUME REQUIRED FOR STORAGE (mL)** |
| PBMC Cryopreservation | CSR | CSR | Na Hep |  | 40 |  |  | 40 |  | 40 | 40 | 40 |
| Serum for storage/redistribution | CSR | CSR | SST |  | 7 |  |  | 7 |  | 7 | 7 | 7 |

CSR = Central Specimen Repository

HVTN Laboratory Program includes endpoint laboratories at Richmond, Duke, FHCRC, and SAIL-NICD. Richmond = Viral and Rickettsial Disease Laboratory, California Department of Health Services (Richmond, California, USA); Duke = Duke University Medical Center (Durham, North Carolina, USA); FHCRC/UW = Fred Hutchinson Cancer Research Center/University of Washington (Seattle, Washington, USA); SAIL-NICD = South African Immunology Laboratory–National Institute for Communicable Diseases (Johannesburg, South Africa)

1. Procedures at HVTN CRS

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Visit: | 01[[16]](#footnote-11)  | 02 | 03 | 04 | 05 | 06 | 07 | 8 | 9 | Post |
| Day: |  | D0 | D14 | D28 | D42 | D84 | D98 | D168 | D364 |  |
| Month: |  | M0 | M0.5 | M1 | M1.5 | M3 | M3.5 | M6 | M12 |  |
| Procedure | Scr. | VAC1 |  | VAC2 |  | VAC3 |  |  |  |  |
| Study procedures[[17]](#footnote-12) |  |  |  |  |  |  |  |  |  |  |
| Signed screening consent (if used) | X | — | — | — | — | — | — | — | — | — |
| Assessment of understanding | X | — | — | — | — | — | — | — | — | — |
| Signed protocol consent and extended safety surveillance consent | X | — | — | — | — | — | — | — | — | — |
| Medical history  | X | — | — | — | — | — | — | — | — | — |
| Complete physical exam | X | — | — | — | — | — | — | — | — | — |
| Abbreviated physical exam | — | X | X | X | X | X | X | X | X | — |
| Risk reduction counseling | X | X | X | X | X | X | X | X | X | — |
| Pregnancy prevention assessment[[18]](#footnote-13) | X | X | X | X | X | X | X | X | X | — |
| Behavioral risk assessment | 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 | — | — |
| 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[[19]](#footnote-14) | X | — | — | — | — | — | X | X | X | — |
| Confirm HIV test results provided to participant | — | X | — | — | — | — | — | — | — | — |
| Local lab assessment |  |  |  |  |  |  |  |  |  |  |
| Urine dipstick | X | — | X | — | — | — | — | — | — | — |
| Pregnancy (urine or serum HCG)[[20]](#footnote-15) | X | X | — | — | — | X | — | X | X | — |
| CBC, differential, platelet | X | — | X | — | — | — | X | — | — | — |
| Chemistry panel  | X | — | X | — | — | — | X | — | — | — |
|  Syphilis, Hepatitis B, Hepatitis C | X | — | — | — | — | — | — | — | — | — |
| Vaccination procedures |  |  |  |  |  |  |  |  |  |  |
| Vaccination[[21]](#footnote-16) | — | X | — | — | — | X | — | X | — | — |
| Reactogenicity assessments[[22]](#footnote-17) | — | X | — | — | — | X | — | X | — | — |
| Poststudy |  |  |  |  |  |  |  |  |  |  |
| Unblind participant  | — | — | — | — | — | — | — | — | — | X |

1. [↑](#endnote-ref-1)
2. [↑](#endnote-ref-2)
3. [↑](#endnote-ref-3)
4. [↑](#endnote-ref-4)
5. [↑](#endnote-ref-5)
6. Shipping Location is the location to which the specimen is shipped for processing (this location may be the same as the Assay Location). [↑](#footnote-ref-1)
7. CL: Central Laboratory; CSR: Central Specimen Repository; [↑](#footnote-ref-2)
8. At Visit 01, ELISA (& Western Blot, if indicated) to be performed at local lab or at CL; for all other visits, ELISA & Western Blot to be performed at CL-Richmond (& optionally, at HVTU labs). [↑](#footnote-ref-3)
9. If assay is positive at Visit 01, apply local laboratory standard of confirmation of EIA-positive serology; if positive at visits other than Visit 01, CL-Richmond to proceed with HVTN algorithm to determine HIV infections. [↑](#footnote-ref-4)
10. Abbott HIV-1 ELISA on Day 364 [↑](#footnote-ref-5)
11. Shipped overnight to CL-Richmond; test to be performed if clinically indicated. [↑](#footnote-ref-6)
12. Serum sample from subjects with fever >38°C or symptoms of viral infection within 7 day, or neurological symptoms within 28 days, s after any dose of vaccine [↑](#footnote-ref-7)
13. Refer to Appendix F [↑](#footnote-ref-8)
14. To be drawn if EBV transformation drawn at Visit 01 is not viable at the time of Visit 02. [↑](#footnote-ref-9)
15. Shipped fresh to CL-Duke for cryopreservation and future analyses. [↑](#footnote-ref-10)
16. Screening may occur over the course of several contacts/visits up to and including day 0 prior to vaccination. [↑](#footnote-ref-11)
17. For specimen collection requirements, see Appendix E. [↑](#footnote-ref-12)
18. Pregnancy prevention compliance occurs only with participants who were born female and are capable of becoming pregnant. [↑](#footnote-ref-13)
19. Includes pre-test counseling. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. [↑](#footnote-ref-14)
20. For a participant who was born female, pregnancy test must be performed on the day of vaccination prior to vaccination. Pregnancy test to determine eligibility may be performed at screening or on day 0 prior to first vaccination. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test. [↑](#footnote-ref-15)
21. Blood draws required at vaccination visits must be performed prior to administration of study product; however, it is not necessary to have results prior to administration. Lab tests may be drawn within the 3 days prior to vaccination. [↑](#footnote-ref-16)
22. Reactogenicity assessments performed daily for at least 3 days postvaccination (see Section 9.8). [↑](#footnote-ref-17)