HIV VACCINE
TRIALS NETWORK

PROTOCOL

HVTN 121

A phase 1b open label clinical trial to evaluate HIV-1 neutralization antibody breadth in response to HIV gp120 protein vaccine in HIV-uninfected adults with quiescent Systemic Lupus Erythematosus

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Division of AIDS (DAIDS)
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Contents

1 Ethical considerations

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

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

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

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

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

- Participants who become HIV-infected during the trial are referred to medical practitioners to manage their HIV infection and to identify potential clinical trials they may want to join. If a program for ART provision is not available at a site and ART is needed, a privately established fund will be used to pay for access to treatment to the fullest extent possible.

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

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

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

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

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

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

2 IRB/EC review considerations

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

2.1 Minimized risks to participants

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

This protocol minimizes risks to participants by (a) correctly and promptly informing participants about risks so that they can join in partnership with the researcher in recognizing and reporting harms; (b) respecting local/national blood draw limits; (c) performing direct observation of participants postvaccination and collecting information regarding side effects for several days postvaccination; (d) having staff properly trained in administering study procedures that may cause physical harm or psychological distress, such as blood draws, vaccinations, HIV testing and counseling and HIV risk reduction counseling; (e) providing HIV risk reduction counseling and checking on contraception use (for persons assigned female at birth); and (f) providing safety monitoring.

2.2 Reasonable risk/benefit balance

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

In all public health research, the risk-benefit ratio may be difficult to assess because the benefits to a participant are not as apparent as they would be in treatment protocols, where a study participant may receive therapeutic benefit from the experimental treatment for their illness. However, this protocol is designed to minimize the risks to participants while maximizing the potential value of the knowledge it is designed to generate.

2.3 Equitable participant selection

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

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

2.4 Appropriate informed consent

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

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

2.5 Adequate safety monitoring

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

This protocol has extensive safety monitoring in place (see Section 11). Safety is monitored daily by HVTN Core and routinely by the HVTN 121 Protocol Safety Review Team (PSRT). In addition, the HVTN Safety Monitoring Board (SMB) periodically reviews study data.

2.6 Protect privacy/confidentiality

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

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

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

3 Overview

Title

A phase 1b open label clinical trial to evaluate HIV-1 neutralization antibody breadth in response to HIV gp120 protein vaccine in HIV-uninfected adults with quiescent Systemic Lupus Erythematosus

Primary objectives

To evaluate the breadth and potency of HIV-1 neutralizing antibody (nAb) responses and

To examine the safety and tolerability of AIDSVAX® B/E in a population of participants diagnosed with Systemic Lupus Erythematosus (SLE) who have stable disease

Study product and route of administration

- **AIDSVAX® B/E:** a bivalent HIV-1 vaccine to be provided by Global Solutions for Infectious Diseases (GSID). The vaccine consists of 300 mcg of subtype B (MN) HIV gp120 glycoprotein and 300 mcg of subtype E (A244) HIV gp120 glycoprotein adsorbed onto 600 mcg of aluminum as aluminum hydroxide gel suspension as adjuvant. Vaccine will be injected IM (1 mL) into the deltoid muscle at Day 0 and Months 1 and 6. The vaccine was originally developed and manufactured by Genentech Inc. The development and manufacturing rights were subsequently transferred to VaxGen, Inc. and finally transferred to its current developer, GSID.

Table 3-1 Schema

	Injection schedule in months		
N	Month 0 Day 0	Month 1 Day 28	Month 6 Day 168
16	AIDSVAX® B/E	AIDSVAX® B/E	AIDSVAX® B/E

Participants

16 low-risk, HIV-1–uninfected volunteers aged 18 to 50 years, diagnosed with SLE who have quiescent disease at the time of enrollment

Design

Open label trial

Duration per participant

12 months of scheduled clinic visits

Estimated total study duration

20 months (includes enrollment and follow-up)

Investigational New Drug (IND) sponsor

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

Study product provider

- AIDSVAX® B/E: GSID (South San Francisco, California, USA)

Core operations

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

Statistical and data management center (SDMC)

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

HIV diagnostic laboratory

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

Endpoint assay laboratories

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

Study sites

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

Safety monitoring

HVTN 121 PSRT; HVTN SMB

3.1 Protocol Team

Protocol leadership

Chair	M. Anthony Moody Duke University 919-668-2551 tony.moody@duke.edu	*Statistician*	Abby Isaacs SCHARP, FHCRC 206-667-7919 aisaacs@fredhutch.org
Co-chair	Paul Goepfert University of Alabama 205-975-5667 paulg@uab.edu	*Medical officer*	Laura Polakowski DAIDS, NIAID 240-627-3040 laura.polakowski@nih.gov
Protocol Team leader	Cecilia Morgan HVTN Core, FHCRC 206-667-5875 cmorgan@fredhutch.org	*Laboratory lead*	Georgia Tomaras HVTN Laboratory Program, Duke University 919-681-5598 georgia.tomaras@duke.edu

Other contributors to the original protocol

Core medical monitor	Carmen Paez HVTN Core, FHCRC	*Clinical safety specialist*	Jill Zeller HVTN Core, FHCRC
Clinical trial investigator	Ankoor Shah Duke University	*Clinical trials manager*	Shelly Ramirez HVTN Core, FHCRC
Study product developer representative	Carter Lee GSID	*Study product developer representative*	Vineeta Gulati GSID
Laboratory protocol operations manager	On Ho HVTN Laboratory Program, FHCRC	*SDMC Associate director of lab science*	April Randhawa SCHARP, FHCRC
Regulatory affairs associate	Denelle Reilly HVTN Core, FHCRC	*Clinical data manager*	Claire Chapdu SCHARP, FHCRC
Clinic coordinator	Amanda Stemke Duke University	*Protocol development manager*	Ramey Fair HVTN Core, FHCRC
Community Advisory Board (CAB) member	Terl Paul Gleason Duke University CAB	*DAIDS protocol pharmacist*	Oladapo Alli DAIDS, NIAID 240-627-3593
Community educator/recruiter	Julieta Giner Duke University	*Community engagement unit representative*	Gail Broder HVTN Core, FHCRC
		Technical editor	Richa Chaturvedi HVTN Core, FHCRC

4 Background

4.1 Rationale for trial concept

The search for an effective HIV-1 vaccine is one of the top priorities of current research efforts (4). Despite decades of research, an HIV-1 vaccine that induces robust nAbs and prevents infection has not been achieved (5). Antibodies with the ability to block HIV-1 infection *in vitro* are called nAbs, and antibodies that do this potently and against a large number of diverse HIV-1 strains are called broadly neutralizing antibodies (bnAbs). A number of bnAbs against HIV-1 have been found, and while some of them have been shown to block infection after passive transfer in nonhuman primate models (6), our ability to routinely induce such antibodies through vaccines has not been successful (5, 7). Finding ways to elicit those kinds of antibodies is a major focus of HIV-1 vaccine development.

BnAbs against HIV-1 have a number of common characteristics that are unusual for vaccine-induced antibodies, including at least one of the following: long, hydrophobic complementarity-determining region 3 loops; high mutation frequency; and/or autoreactivity (8). These characteristics are, however, frequently found in autoantibodies derived from those with autoimmune diseases like systemic lupus erythematosus (SLE). Moreover, these antibody characteristics of bnAbs are typical of antibodies controlled by host tolerance mechanisms (9). A number of investigators have noted that coincident SLE and HIV-1 infection is rare (10), while others have suggested that the kinds of antibodies that are made during SLE might be protective against HIV-1 infection (11). This has led to a hypothesis that antibody production in patients with autoimmune diseases like SLE and defective immune tolerance mechanisms similar to what SLE patients are known to exhibit may permit the development of antibodies with enhanced ability to block HIV-1 infection that are not normally produced by individuals without autoimmune disease (12). Based on these data, a primary hypothesis of this study is that an HIV-1 vaccine given to participants with SLE will elicit antibodies with characteristics of bnAbs, including increased neutralization breadth and/or gene usage and maturation patterns similar to bnAbs that have arisen during HIV-1 infection. It is currently unknown whether an HIV-1 vaccine will enhance the amount or activity of potentially protective HIV-1 antibodies in patients with SLE.

Preliminary studies in mice including wild type and knock-in models of bnAbs have repeatedly demonstrated that antibodies of this type are controlled by tolerance mechanisms (9, 13-18). There are multiple murine models that have been used to examine the pathophysiology of SLE including therapeutic interventions (19), but such models do not have human B or T cell repertoires, suggesting that such models will be of limited use in evaluating vaccines that will be given to humans.

In support of the idea that SLE may be permissive for the development of bnAbs, an individual has been studied who developed SLE after becoming infected with

HIV-1. Although not protected from infection, over time this individual developed bnAbs and was able to control the virus without antiretroviral therapy (ART) (20). A monoclonal antibody (mAb), CH98, was isolated from blood B cells from this individual; this antibody broadly neutralized HIV-1 by binding to the HIV-1 gp120 Env CD4 binding site and displayed characteristics shared among HIV-1 bnAbs and antibodies commonly identified in autoimmune disease (long complementarity-determining region 3 loops and high mutation frequency). In particular, antibody CH98 is polyreactive (it reacts with more than 90% of 9,400 human host cellular antigens), and it specifically binds to double-strand DNA (dsDNA), a specificity that is commonly induced during SLE (21) and which was present in this patient whose plasma also contained anti-dsDNA autoantibodies (20).

While no human trial of HIV-1 vaccine candidates has elicited bnAbs, a number of results have suggested that an effective HIV-1 vaccine might be possible. The RV144 ALVAC-prime AIDSVAX-boost phase 2b vaccine efficacy trial, performed on HIV-uninfected individuals in Thailand, demonstrated 31% efficacy against acquisition of infection in low-risk subjects (22). The correlates of risk analysis showed that protection from infection correlated with antibodies directed against HIV-1 envelope protein (23). This has raised the possibility that with proper modification for enhanced vaccine efficacy, this vaccine could be made effective for general deployment.

One of the immunogens used in the RV144 trial, Env gp120 AE.A244 has been shown to bind to the unmutated common ancestor of V1V2 glycan epitope bnAbs CH01-04 (24) with an affinity sufficient to stimulate B cells bearing such antibodies to undergo affinity maturation (25, 26). This raises the hypothesis that this immunogen could stimulate precursors of V1V2 glycan epitope bnAbs to expand following vaccination. In addition, this immunogen has also been associated with the elicitation of CD4 binding site antibodies: RV144 vaccinees who were boosted 6-8 years after the initial RV144 vaccine regimen (a trial called RV305) have been recently studied, and at a level of approximately 3 per million B cells, the vaccine boosts with either ALVAC + AIDSVAX® B/E or AIDSVAX® B/E alone induced the expansion of B cells that have characteristics suggesting they are early members of heavy chain complementarity determining region 3 (HCDR3)-binder CD4 binding site bnAb lineages (27). B cells in such lineages produce antibodies with long HCDR3 regions that differentially bind to wild type Env but not to Env with a deletion of isoleucine at amino acid position 371, and that neutralize one or more tier 2 (difficult-to-neutralize) HIV-1 strains. These two lines of evidence suggest that in the right immunologic setting, a better quality of serum nAbs and/or a higher frequency of B cells with characteristics of bnAb precursors might be elicited by vaccination. Thus, one of the immunogenicity hypotheses of this protocol is that SLE vaccinees will have qualitatively better gp120 antibody responses than were found in RV144 vaccinees, as tested by serum neutralization. In addition, another hypothesis is that repertoire analysis of memory B cells and plasmablast / plasma cells induced by gp120 in SLE patients will demonstrate an expansion of the pool of V1V2 glycan epitope and/or CD4 binding site bnAb precursors, that this expanded pool

will consist of antibodies that are more mutated than those found in RV305, and that these antibodies will demonstrate a greater degree of neutralization breadth (9, 20). To test this, the analysis will quantify the frequency of V1V2 glycan epitope and CD4 binding site bnAb precursors in memory B cells and plasmablast / plasma cells in SLE patients vaccinated with AIDSVAX® B/E to determine if the induced gp120 response in SLE vaccinees is enhanced, as manifested by induction of bnAbs.

4.1.1 Rationale for HIV-1 immunization for persons with SLE

It is unlikely that the vaccine regimen used in this study will provide direct protection against HIV-1 infection to participants. The primary immunological objective of this study is to determine whether an HIV-1 vaccine that can engage precursors of V1V2 glycan epitope bnAbs and has been associated with eliciting antibodies directed at the CD4 binding site can more robustly expand those pools of B cells in the presence of altered immune tolerance.

The specific rationale for performing the study in a group of persons with SLE is that 1) HIV-1 bnAbs have characteristics indicating they arose from B cells under immune tolerance control (i.e., lacking tolerance to self antigens) and persons with SLE are known to exhibit this type of altered immune tolerance, 2) several investigators have noted an underreporting of coincident SLE and HIV-1, and have suggested that SLE may permit protective immune responses and 3) a bnAb cross reactive with dsDNA was isolated from a person who had both SLE and HIV-1 (20, 28, 29). In addition, a recent study showed that autoimmune-prone mice immunized with HIV-1 Env were able to develop neutralization breadth (30).

To date, no HIV-1 vaccine trial has been performed in patients with SLE. While it is likely that patients with SLE and other autoimmune diseases will be one of many targeted populations (along with pregnant women and children) for any widely deployed HIV-1 vaccine, the primary purpose of this study is investigating immunological questions related to HIV-1 vaccine response in the setting of altered immune tolerance, as in patients with SLE. If SLE patients demonstrate production of nAbs upon receipt of an HIV-1 vaccine, further evaluation of the immunological conditions present in these patients might reveal mechanisms that can be simulated in healthy individuals with a specific type of vaccine transient immune modulation (vTIM), which consists of the use of immune system-modulating drugs (e.g., chloroquine, monoclonal antibodies used in the treatment of cancer that alter immune tolerance) given at or around the time of immunization that can permit antibody responses typically suppressed under tolerance control in healthy individuals. Importantly, this study might identify a critical pathway of immune tolerance for which no drugs currently exist, and could provide crucial data that support the development of novel directed therapies that permit protective HIV-1 responses in the vTIM setting.

In performing the first HIV-1 vaccine trial in SLE patients, it is appropriate to use a vaccine with the most extensive safety data and a non-live vaccine product that

is generally considered safe for persons with SLE and fits the criteria outlined in the EULAR recommendations for vaccination of patients with autoimmune inflammatory rheumatic diseases (31, 32). For this study, the bivalent HIV-1 envelope (Env) protein vaccine, AIDSVAX® B/E, will be used; this vaccine has been administered to > 10,000 human volunteers and has been demonstrated to be safe (22, 33). Furthermore, this vaccine was a component of the only HIV-1 vaccine trial to show efficacy, the ALVAC-prime/AIDSVAX® B/E-boost RV144 trial (22). Using the alum-adjuvanted AIDSVAX® B/E vaccine in this trial will also present an opportunity to directly evaluate the effect of an alum-adjuvanted vaccine on immune system activation in people with SLE.

4.1.2 Safety considerations for immunization of persons with SLE

Data on the safety of vaccines in persons with SLE are readily available. The majority of published guidelines have emphasized the safety of killed or subunit vaccines in autoimmune disease patients (31, 32, 34, 35); and while live attenuated vaccines should be used cautiously, they also have been demonstrated to be safe in this population (34).

Vaccination of persons with SLE has been studied using a variety of immunogens and study designs. Between 1978 and 2016, there were at least 40 published studies examining vaccination in adults and children with SLE. The studies examined 2,595 persons with SLE who were vaccinated, 287 persons with SLE who were not vaccinated as a part of the published studies, and 1,169 vaccinated controls (36-77). The methods used to evaluate study participants were variable, with 29/40 using the SLE Disease Activity Index (SLEDAI). A summary of the findings follows.

- 11 studies that compared vaccinated and unvaccinated persons with SLE (including 5 randomized controlled trials) showed no difference in disease activity between groups (36-38, 42, 46, 51, 57, 67, 72, 73, 76, 77).

- 9 studies that compared disease activity pre- and post-vaccination in persons with SLE showed no significant difference in disease activity (48, 49, 52, 53, 57, 58, 63, 64, 69).

- 21 studies (including some of the above-noted studies) examined SLE disease flares post-vaccination (40, 47, 54, 56, 58, 59, 61, 67, 68).
    - 13 reported that the rate of flares among vaccinated SLE patients was similar to that among unvaccinated SLE patients (40, 42, 47, 51, 54, 56-59, 61, 67, 68, 72, 77).
    - 4 studies each reported one vaccinated SLE participant who experienced a single flare (3 glomerulonephritis, 1 optic neuritis, 1 unspecified) (55, 62, 74, 75).

- 1 reported 7/62 SLE participants experienced a flare (1 with a severe flare of glomerulonephritis and 6 with mild to moderate disease flares of varying symptoms post-influenza vaccination) (71).
- 1 recruited SLE patients with SLEDAI < 4, and reported 3/28 participants experienced a flare (rash/alopecia, photosensitivity/discoid rash, polyarthritis) (60).
- 1 reported 4/20 participants with flare (joint symptoms, vasculitis, altered affect, increased nephritis) (41).
- 1 reported 20/72 participants with moderate to severe flares; this study enrolled participants with moderate to high disease activity (41/72 participants with ≥ 6 SLEDAI at baseline) (50).

In summary, the findings of these studies suggest that vaccines are generally safe and well tolerated by persons with SLE, but that safety concerns do exist and that careful study design, recruiting of participants with low disease activity at baseline, and monitoring is important.

The most commonly used adjuvant for vaccines in the studies referenced above was alum. Until recently, alum was the only adjuvant licensed for use in the US (78), and alum remains the most commonly used adjuvant for recommended vaccines in the US for children (79) and adults (80). Studies in murine models of SLE have suggested that alum could exacerbate SLE-like disease (81), but studies in humans are limited. Direct study of the effect of vaccines in patients with autoimmune disease has focused on safety and immunogenicity measures, particularly in light of increased use of immunosuppressant medications in the treatment of autoimmune disease. An observational study of 218 autoimmune-disease patients immunized against influenza detected a slight increase in autoantibodies, although the findings were not statistically significant (82); data from this study suggested that anti-cardiolipin antibodies may have transiently risen, but that they subsequently fell below baseline levels upon 6-month follow-up (82). Another observational study of 1,668 patients found that influenza vaccination was immunogenic and that moderate and severe side effects were not observed, but that vaccine response was blunted in patients with autoimmune disease (66). A Serbian study of autoimmune disease patients noted that 47 influenza-immunized patients had a decreased incidence of respiratory infections compared with 52 unimmunized patients; no increase in underlying autoimmune phenomena were observed (38).

The HIV-1 vaccine product to be used in this clinical trial (AIDSVAX® B/E consisting of envelope (Env) gp120 of HIV MN clade B and HIV A244 clade CRF01_AE) is formulated in alum, and was previously used in other large-scale human trials, including RV144, the large-scale efficacy trial of AIDSVAX® B/E among 16,402 healthy men and women in Thailand, and VAX003, an efficacy trial of AIDSVAX® B/E among 2,527 injection drug users in Thailand (22, 33). In RV144, 2 participants (of 16,402 total) developed autoimmune disease while enrolled and both received at least part of the complete vaccine regimen (Kim JH

and Haynes BF, unpublished observations). One participant who developed immune thrombocytopenic purpura more than one year after the complete vaccine regimen did not have detectable autoantibodies before or after the vaccination schedule. The other participant was diagnosed with SLE during the course of the vaccine regimen and had antibodies against Sjögren's syndrome A (SSA) (value 215) and centromere B before vaccination; this participant was positive only for SSA (value 142) after vaccination, showing that the vaccine product to be used in this protocol did not induce autoantibodies in these susceptible subjects. However, the second individual was diagnosed with SLE after 3 vaccinations with a live canarypox (ALVAC) vector and one vaccination with B/E gp120, and the final trial ALVAC/AIDSVAX immunization was not given. Importantly, neither participant experienced any vaccine-related adverse events (AEs). In this study, no live vector vaccines will be used, only AIDSVAX® B/E protein formulated with alum. This study plan is consistent with vaccine guidance for participants with SLE and will use both an HIV-1 immunogen and adjuvant with the greatest amount of safety data in human participants.

One important outcome of this trial will be a prospective assessment of the effect of this alum-adjuvanted vaccine on immune system activation in SLE patients. We plan to assess this using state of the art assays including systemic cytokine measurements, immune cell phenotyping, and single cell sorting of B and T cells to quantify vaccine-induced transcripts. Immune cell activation will be assessed by quantitative polymerase chain reaction (qPCR). We plan to assess changes to the frequency and activation state of both B and T cell populations for this cohort and a group of historical control subjects drawn from a prior study of this vaccine formulation—specifically, RV328, a phase I/II trial assessing the immunogenicity of AIDSVAX® B/E among 40 HIV-uninfected individuals in Thailand. Data obtained for the safety and immune activation outcomes in RV328 will be compared to the AE reports and immunogenicity data obtained in this study, to compare the effects of alum-adjuvanted vaccine administration between healthy subjects and SLE patients. After correction for multiple comparisons, this small study will not be able to detect statistically significant differences between those with SLE and the historical controls. In addition, this study is not powered to identify rare safety events. However, this study will provide a first and critical dataset for participants with SLE to which future HIV-1 vaccine/adjuvant candidates can be compared. In addition, differences observed in this study will provide a dataset to help guide development of future studies and for the assessment of future vaccine candidates in patients with SLE. Given the importance of vaccines in prevention of disease in SLE patients (31, 32, 34, 35, 83), these data will fill a critical gap in current knowledge and inform risk assessments of current and future vaccines. By using the non-replicating component of the only HIV-1 vaccine regimen to have shown any efficacy in preventing HIV-1 transmission, we will obtain information about alum-adjuvanted vaccine immune activation in persons with SLE, and also assess how individuals with SLE can respond to a protein-based HIV-1 vaccine.

4.1.3 Potential impact of this study on development of future HIV-1 vaccine candidates

This trial aims to provide information that will inform vaccine design for people who do not have SLE by quantifying the effect that altered immune tolerance has on HIV-1 bnAb development. It has been observed that bnAbs against HIV-1, and specifically antibodies reactive with many different virus subtypes, are not made by the majority of infected patients. When such antibodies are made, they usually occur after several years of infection (84). These bnAbs have a number of characteristics commonly found in autoantibodies, such as long and hydrophobic antigen binding loops, high levels of somatic mutation, and/or polyreactivity with human antigens (85). Antibodies with these characteristics are usually under tolerance control during B cell development and maturation (9, 12, 15), and antibodies reactive with self-antigens are commonly found in patients with defects in immune tolerance (eg, autoimmune diseases such as SLE) (86, 87). Importantly, studies with bnAb knock-in mice have shown that indeed some bnAbs are directly eliminated by numerous tolerance mechanisms including deletion, anergy and receptor editing (9, 15, 17).

In addition, several investigators have noted an underreporting of coincident SLE and HIV-1 infection (10, 29, 88, 89) and early in the HIV-1 epidemic it was speculated that antibody responses in SLE may be protective against HIV-1 infection (11). To date, there have been no prospective studies of either HIV-1 infection or vaccination in patients with autoimmune diseases; thus, whether patients with autoimmune diseases can make qualitatively or quantitatively better responses to HIV-1 vaccine antigens, or to any other type of vaccine, is unknown.

There are, however, data that suggest SLE could be permissive for the development of bnAbs against HIV-1. In mouse studies of bnAb development, B cells expressing these antibodies were subject to strict tolerance control (15, 17). BnAb 2F5 was shown to react with a human antigen; mice that have the same antigenic epitope restrict the creation of 2F5-epitope specific antibodies while opossums that lack the same epitope are not restricted (90). Taken together, these data suggest that some bnAbs are under similar tolerance controls in humans and would be difficult to elicit with vaccines (9, 12, 18). This is corroborated by the fact that none of the large-scale HIV-1 vaccine trials in humans have elicited bnAbs (91). In order to make an effective vaccine against HIV-1, we must determine the roadblocks and potential solutions in order to guide future vaccine development. If patients with SLE are capable of making a better antibody response after HIV-1 vaccination, this will suggest that modulation of tolerance may be required to induce those kinds of responses in people without autoimmune disease.

In support of this idea, a recently published study has shown that the development of bnAbs by individuals with chronic HIV-1 infection is associated with the presence of plasma autoantibodies and with a lower frequency of regulatory CD4+ T cells, a higher frequency of circulating memory T follicular helper (Tfh) CD4+ cells, and a higher T regulatory (Treg) cell level of programmed cell death–

1 expression (92). This vaccine trial in participants with SLE will allow us to assess for these same alterations of T cell populations in this group of vaccine recipients. The data generated by this study will provide critical information as to whether naturally occurring variations in immune tolerance control, as exist in SLE, are permissive for bnAb development.

Thus, a critical question to be posed by this vaccine study is whether the AIDSVAX® B/E immunogen can induce nAbs in patients with known SLE and whether these antibodies can block infection *in vitro*. This is particularly important to test for the AIDSVAX® B/E immunogen, as it was part of the vaccine regimen that induced a modest degree of protection in the RV144 trial (22). Of note, the two participants in RV144 who developed autoimmune disease were studied and did not develop neutralizing breadth in any of the samples tested. Neither were followed beyond the end of the study, and neither were recruited into the follow-on studies, so data collected in this study could provide valuable information about the effects of altered immune tolerance on HIV vaccine immunogenicity. If bnAbs are produced by any SLE patients in this study, we will further evaluate the effect of altered immune tolerance on their production. By measuring potential genetic influences, the specific cytokine milieu, differences in B-cell and T-cell populations, differences in innate immunity, etc., we can attempt to assess for differences that might exist between SLE patients who develop bnAbs and healthy patients who do not. If we are able to determine what is different in those with SLE, we can try simulating these differences in animals to evaluate whether specific interventions with specific effects on immune tolerance induce bnAb development in healthy (non-autoimmune) animals, and—if successful—work towards implementing similar regimens in humans. The results of this study could help guide the development of future vaccine candidates and adjuvant systems that could induce such responses in the general population.

4.2 AIDSVAX® B/E

AIDSVAX® B/E is a bivalent HIV gp120 glycoprotein originally developed and manufactured by Genentech Inc. The development and manufacturing rights were subsequently transferred to VaxGen, Inc. and finally transferred to its current developer, GSID. It is a purified mixture of gp120 proteins produced by recombinant DNA procedures using Chinese hamster ovary (CHO) cell expression. The sequences of MN gp120/HIV-1 and A244 gp120/HIV-1 are expressed as fusion proteins where a 27 amino acid sequence found in the glycoprotein D (gD) of herpes simplex virus type 1 is fused to the amino terminus of each protein. MN and A244 rgp120/HIV-1 are combined to produce the bivalent AIDSVAX® B/E vaccine. AIDSVAX® B/E encompasses both subtype B (MN) and subtype E (A244) proteins that are adsorbed onto 600mcg of aluminum as aluminum hydroxide gel suspension as adjuvant.

4.3 Trial design rationale

In this study, 16 eligible participants, who have a physician-confirmed diagnosis of SLE as defined by the classification criteria established by the ACR (86, 87) and who are free of HIV-1 infection, will be administered three doses of alum-adjuvanted AIDSVAX® B/E. This will be an open-label single arm study. AIDSVAX® B/E has an extensive safety history in clinical trials (93, 94). Given this, as well as the knowledge that no prior AIDSVAX® B/E vaccinees have developed HIV-1 bnAbs, the inclusion of a concurrent non-SLE control group is not felt to be necessary. We expect that all participants without autoimmune disease in a control arm would have a similar response and not produce bnAbs; we do not expect a concurrent control arm of healthy participants to provide additional information beyond what can be obtained with historical controls. The study group will therefore be compared with an historical control group comprised of non-SLE subjects previously enrolled in RV328, a similar study assessing immunogenicity of AIDSVAX® B/E administered at the same time points as proposed in this study (Day 0 and Months 1 and 6), plus additional later time points not proposed in this study.

With regards to RV328, an analysis of all participants found that 0/40 participants (30 vaccinated with AIDSVAX® B/E, 10 with placebo) developed neutralization breadth. Given the small study size, we will include all 30 AIDSVAX® B/E vaccinees in the historical control group. As previously noted, RV328 was performed in Thailand, and thus cannot be matched for ethnicity or country of origin.

As part of the original Center for HIV-AIDS Vaccine Immunology (CHAVI)program, the CHAVI 005 study examined a group of participants with known autoimmune disease to determine if any had undiagnosed HIV-1 infection, and if their plasma had any evidence of existing neutralizing antibodies that could account for the previously noted disparity between SLE and HIV-1 infection. This cohort, including 100 participants without autoimmune disease and 125 participants with SLE, was recruited from the Duke Lupus Clinic between 2005-2011. The CHAVI program tested this cohort using both HIV-1 antibody and viral load assays and found that none of the participants were HIV-1-infected. Testing of a subset of the participants did not reveal evidence of HIV-1 neutralizing antibodies or reactivity with HIV-1 Env proteins, although it should be noted that the study participants did not receive any HIV-1 vaccinations. Samples from this study are available for testing using the same assays planned for the present study, and for all participants, there are plasma, serum, and PBMC stored in the CHAVI Repository. This cohort was drawn from the same patient population at Duke that will be recruited for this study, and because the second of two sites participating in this study is in Alabama, the demographics of the two populations is likely to be similar. We can therefore use the SLE patients in the CHAVI 005 study as unvaccinated SLE controls, serving as a cross-sectional comparison group.

The primary outcome is to evaluate whether persons with SLE vaccinated with an HIV-1 vaccine will develop HIV-1 nAbs with greater breadth and potency than persons without SLE. In addition, our immunogenicity hypotheses are that this cohort of participants with SLE will make a qualitatively and quantitatively superior antibody response against HIV-1. An additional secondary outcome will address the hypothesis that the vaccine regimen will be safe and well tolerated by participants. The proposed number of participants is not sufficiently powered to detect uncommon or rare events. Participants will be monitored for sentinel events indicative of SLE disease activation (ie, SLE flare); detection of an SLE flare will trigger additional review.

4.3.1 Dose (amount and number)

The AIDSVAX® B/E dose of 600 mcg / 1 mL is the same as was used in the RV328, RV144 (22) and VAX003 (33) trials. The sequence of AIDSVAX® B/E immunizations is similar to that given in all three of these trials, however, we have reduced the number of vaccinations to three (3) to reduce the time needed for completion of the study.

4.3.2 Schedule

The schedule for AIDSVAX® B/E was chosen to be consistent with, but shorter than, the schedule used in RV328, RV144 (93) and VAX003 (33). The present study will only use the first 3 immunization timepoints: Day 0 and Months 1 and 6.

4.4 Clinical studies

4.4.1 AIDSVAX® B/E

The AIDSVAX® B/E (HIV B.MN gp120/HIV AE.A244) gp120 vaccine preparation used in this study has been used in 3 phase 3 human studies (22, 33, 95). In these trials, more than 9000 participants received the vaccine product. In all trials, this vaccine was found to be safe and well tolerated, with observed adverse vaccine reactions being primarily local reactogenicity (eg, pain or inflammation at the injection site). Other reported side effects of this vaccine include induration, erythema, edema, and subcutaneous nodules at the injection site. Systemic side effects include headache, rash, fever, fatigue, malaise, myalgia, or allergic reactions. Administration of related vaccine preparations have been given to 287 HIV-1–infected individuals without evidence of adverse outcome (96).

One serious adverse event (SAE) was reported in the phase I/II trial, RV328, conducted more recently in Thailand. It was deemed related to AIDSVAX® B/E vaccine. A participant developed a case of severe hypersensitivity reaction after receiving the 4th and final dose of AIDSVAX® B/E. Within 3 minutes of receiving the vaccine, the participant developed a generalized pruritic rash, facial

swelling, and malaise, but had no difficulty breathing or hypotension. This individual had received 3 prior vaccinations with AIDSVAX®B/E with no concomitant symptoms. The participant was treated and recovered completely within a few hours.

In one of the phase 3 studies of this vaccine, VAX003, the vaccine product was injected 7 times over the course of the protocol (at months 0, 1, 6, 12, 18, 24, and 30). This protocol (HVTN 121) has a planned course of 3 vaccinations, thus this study will not exceed the prior experience with AIDSVAX® B/E.

Prior vaccine studies using AIDSVAX® B/E did not induce bnAbs either following canarypox priming, as in the RV144 trial (22), or when administered alone, as in the VAX003 trial (33). In these 2 studies, nAbs were restricted to easy-to-neutralize (tier 1) isolates from clade AE circulating recombinant form CRF01_AE (91). Antigenicity studies of the AIDSVAX® B/E immunogen have shown that Env variable loop 1 and 2 (V1V2) glycan bnAbs such as PG9 and CH01 bind readily to epitopes expressed on the AE.A244 gp120 vaccine components, and the putative naïve B cell receptor of the CH01 bnAb lineage also binds well to the AE.A244 gp120 (97). Thus, the AIDSVAX® B/E immunogen is antigenic for V1V2 bnAbs, but no plasma V1V2 bnAb activity was induced in the RV144 vaccine trial (91). Thus, a secondary hypothesis to be tested in this trial is whether the AIDSVAX® B/E immunogen can induce V1V2 glycan nAbs when administered to trial participants with SLE.

Intriguingly, another vaccine trial (VAX003) administered the same AIDSVAX® B/E immunogen used in the boost phase of RV144 and produced robust Env antibody responses that were higher than those seen in RV144 (33). Despite these responses, VAX003 did not prevent HIV-1 acquisition in a high-risk population of intravenous (IV) drug users in Thailand. It has recently been found that the use of ALVAC and a prime and boost in RV144 induced higher levels of IgG3 Env antibodies than in VAX003 and these IgG3 antibodies against V1V2 correlated with decreased transmission risk (98). Thus, the RV144 vaccine may have been protective because of induction of IgG3 V1V2 responses, but efficacy was limited by minimal potency and short duration of the induced antibody responses (98). These data would suggest that ALVAC priming may be required for V1V2 responses in adults lacking autoimmune disease, thus it will be important to carefully assess for these responses in patients with SLE receiving AIDSVAX® B/E. Furthermore, given concerns over the use of live vector vaccines in patients with SLE (31, 32), determining whether AIDSVAX® B/E alone can elicit V1V2 responses will guide the deployment of future HIV-1 vaccine candidates in this vulnerable population.

4.5 Potential risks of study products and administration

The vaccine has been extensively tested in healthy populations. Prior work has shown that vaccination of autoimmune disease patients with killed or subunit vaccines are generally well tolerated (99).

Table 4-1 Summary of potential risks of study products and administration

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

* See section 4.1.2 for a review of studies evaluating other vaccines in people with SLE and the potential for exacerbation of autoimmune disease. There are no prior studies evaluating AIDVAX B/E® in participants with SLE or other autoimmune disease, and therefore the risk of exacerbating autoimmune diseases is unknown for this study vaccine.

5 Objectives and endpoints

5.1 Primary objectives and endpoints

Primary objective 1:

To evaluate the breadth and potency of HIV-1 nAb responses

Primary endpoint 1:

Response rates, magnitude and breadth of nAb responses to the vaccine strains and a global panel of heterologous env-pseudotyped viruses at baseline and two weeks after the third vaccination

Primary objective 2:

To examine the safety and tolerability of AIDSVAX® B/E in a population of participants diagnosed with SLE who have stable disease

Primary endpoints 2:

- Frequency and severity of local and systemic reactogenicity signs and symptoms
- Laboratory measures of safety: white blood cells (WBC), neutrophils, lymphocytes, hemoglobin, platelets, ALT, complement, anti-dsDNA titers, urinalysis and spot urine protein:creatinine ratio
- Frequency of adverse events categorized by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class, and MedDRA Preferred Term, severity and assessed relationship to study products; detailed description of all AE meeting DAIDS criteria for expedited reporting
- Measures of SLE disease activity and functional status: Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) and Routine Assessment of Patient Index Data (RAPID3)

5.2 Secondary objectives and endpoints

Secondary objective 1:

To characterize isolated antibodies for evidence of HCDR3-binding CD4 binding site bnAb lineages elicited by the vaccine

Secondary endpoint 1:

The degree of somatic hypermutation, length of antibody binding loops and germline gene usage in participants with SLE compared with historical controls after the third vaccination

Secondary objective 2:

To assess the induction of bnAb precursors

Secondary endpoint 2:

NAb responses to viruses with altered glycosylation, indicative of bnAb precursors, at baseline and two weeks after the second and third vaccinations

Secondary objective 3:

To determine the effect of an HIV vaccine on immune system activation

Secondary endpoint 3:

Vaccine-induced immune activation as assessed by serum cytokine analysis and B and T cell phenotyping, as well as expression of Treg and Tfh markers one week after the second and third vaccinations

Secondary objective 4:

To evaluate the level of HIV-1–specific binding antibody production in response to vaccination

Secondary endpoint 4:

Response rate and magnitude of HIV-1–specific IgG binding antibodies at baseline and two weeks after the second and third vaccinations

Secondary objective 5:

To further characterize the epitopic specificity of HIV-1 binding antibodies

Secondary endpoint 5:

Specificity of antibody responses by epitope mapping of functional and binding antibodies two weeks after the second and third vaccinations

Secondary objective 6:

To determine whether CD4+ T-cell responses are associated with the observed antibody responses

Secondary endpoint 6:

Response rate, magnitude and polyfunctionality of Env-specific CD4+ T cells 2 weeks after the third vaccination

5.3 Exploratory objectives

Exploratory objective 1:

To determine the breadth and potency of the antibody-dependent cellular cytotoxicity (ADCC)-mediating antibody response against HIV-1 to vaccination

Exploratory objective 2:

To determine if there are common genetic mutations in this group of SLE participants

Exploratory objective 3:

To further evaluate immunogenicity of the vaccine regimen, additional immunogenicity assays may be performed, including on samples from other timepoints

Exploratory objective 4:

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

6 Statistical considerations

6.1 Accrual and sample size calculations

Recruitment for this single arm study will target enrolling 16 low-risk, HIV-uninfected adult participants, aged 18-50, who have also been diagnosed with SLE.

The primary purpose of this study is to explore the possibility that AIDSVAX® B/E may induce bnAbs in a population of participants diagnosed with SLE and to closely monitor participant safety. Since enrollment is concurrent with receiving the first study vaccination, all participants will provide some safety data. However, for immunogenicity analyses, it is possible that data may be missing for various reasons, such as participants terminating from the study early, problems in shipping specimens, low cell viability of processed peripheral blood mononuclear cells (PBMCs). Immunogenicity data from 17 phase 1 and 2 phase 2a HVTN vaccine trials, which began enrolling after June 2005 (data as of September 2014), indicate that 15% is a reasonable estimate for the rate of missing data at day 182. For this reason, the sample size calculations in Section 6.1.2 account for 15% of enrolled participants having missing data for the primary immunogenicity endpoint.

6.1.1 Sample size calculations for safety

The goal of the safety evaluation for this study is to identify safety concerns associated with product administration. This participant population is at risk for at least two different categories of AEs—vaccine-related reactogenicity (or other side effects) and the development of a flare of SLE disease activity. For this reason, we will treat these events separately for the following calculations.

6.1.1.1 Vaccine-related AEs

The ability of the study to detect SAEs (see Section 11) can be expressed by the true event rate above which at least 1 SAE would likely be observed and the true event rate below which no events would likely be observed. Specifically, for the vaccine arm of the study (n = 16), there is an 81.5% chance of observing at least 1 event if the true rate of such an event is 10% or more; and there is an 85.1% chance of observing no events if the true rate is 1% or less.

Probabilities of observing 0, 1 or more, and up to 5 or more events among arms of size 16 are presented in Table 6-1 for a range of possible true AE rates. These calculations provide a more complete picture of the sensitivity of this study design to identify potential safety problems with the vaccine.

Table 6-1 Probability of observing 0 events, 1 or more events, and up to 5 or more events, among arms of size 16, for different true event rates

True event rate (%)	Pr(0/16)	Pr(1+/16)	Pr(2+/16)	Pr(3+/16)	Pr(4+/16)	Pr(5+/16)
1	0.851	0.149	0.011	0.001	0	0
5	0.440	0.560	0.189	0.043	0.007	0.001
10	0.185	0.815	0.485	0.211	0.068	0.017

For this study, suspected adverse reactions are any AEs for which there is a reasonable possibility that the vaccine caused the event, suggesting a causal relationship. Using exponential hazard time-to-event methods in simulation (N = 1000), if there is a 5% chance per year of a related non-serious AE, we would be expected, on average, to have 0.8 incidents (95% CI: <1, 2.5) during the 12 months of follow-up in this study. If the AE rate is 7.5%, we would expect, on average, to have 1.1 events (95% CI: <1, 3.2); if the AE rate is 10%, we would expect, on average, to have 1.6 events (95% CI: <1, 3.9).

6.1.1.2 Flare of SLE disease activity

This subject cohort may be expected to have an SLE flare rate as high as 20% (defined as an increase of 4 or more in SLEDAI (100) between study visits), indicating that a more conservative threshold is appropriate. For example, if we base the expected SLE flare rates on the control arm of Ruiz-Irastorza et al (101), where the monthly percentage of patients with flares was 3.9%, we expect a possibly higher rate of SLE flare than that described above. Using exponential hazard time-to-event methods in simulation (N = 1,000), if there is a 3.9% chance per patient-month of flare, we would be expected, on average, to have 6.1 incidents (95% CI 2.1, 10.1) per year of follow-up in this study. If flare events are independent, then there is 14.4% chance of a participant having 2 flare events in one year.

6.1.2 Sample size calculations for immunogenicity

The primary immunogenicity endpoint will be the production of bnAbs. This will be defined as a nAb geometric mean titer (GMT) greater than 100 against a standard HIV-1 pseudovirus panel. The sample size of 16 was selected such that if the true proportion of participants producing bnAbs in this population is at least 10 percent, we will have 81.5% probability of detecting bnAbs in at least one participant. If there is a dropout rate of 10% then we will still have a 77.1% probability of detecting bnAbs in at least one participant (Table 6-2).

Table 6-2 Probability of detecting bnAbs in at least one participant, among different arm sizes, for different true event rates

Number of Participants	True Population Percentage of SLE Participants Producing BnAbs			
	1%	5%	10%	25%
12	0.114	0.460	0.718	0.968
14	0.131	0.512	0.771	0.982
16	0.149	0.560	0.815	0.990
18	0.165	0.603	0.850	0.994

6.2 Randomization

Since there is only one treatment assignment in this study, participants will not be randomized.

6.3 Statistical analyses

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

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

6.3.1 Analysis variables

The analysis variables consist of baseline participant characteristics, safety, and immunogenicity for primary- and secondary-objective analyses.

6.3.2 Baseline comparability

Selection of historical controls from RV328 that were vaccinated and underwent immunogenicity testing on a similar timeline will serve as a suitable non-SLE control group. Although, given the small study population (40 total), all 30 who received AIDSVAX® B/E will be included as comparators.

The 125 SLE patients in the CHAVI 005 study, with similar demographic characteristics to this study population, will serve as a cross-sectional, unvaccinated SLE control group for immunogenicity comparisons.

6.3.3 Safety/tolerability analysis

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

6.3.3.1 Reactogenicity

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

6.3.3.2 AEs and SAEs

AEs will be summarized using MedDRA System Organ Class and preferred terms. Tables will show the number and percentage of participants experiencing an AE within a System Organ Class or within preferred term category by severity or by relationship to study product. For the calculations in these tables, a participant with multiple AEs within a category will be counted once under the maximum severity or the strongest recorded causal relationship to study product.

A listing of SAEs reported to the DAIDS Regulatory Support Center (RSC) Safety Office will provide details of the events including severity, relationship to study product, time between onset and last vaccination, and number of vaccinations received.

6.3.3.3 Local laboratory values

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

For each local laboratory measure, summary statistics will be presented by study cohort and timepoint, as well as changes from baseline for postenrollment values. In addition, the number (percentage) of participants with local laboratory values recorded as meeting Grade 1 AE criteria or above as specified in the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Section 9.8) will be tabulated for each postvaccination timepoint. Reportable clinical laboratory abnormalities without an associated clinical diagnosis will also be included in the tabulation of AEs described above.

6.3.3.4 SELENA-SLEDAI

Box plots will be generated for baseline values and for values measured during the course of the study. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted. Each participant's points will be connected with a line. Summary statistics will be presented by study cohort and timepoint. A listing of participants who discontinue vaccination due to related SLE flares (of any severity), as defined in Appendix G and Section 7.3.3, will also be produced.

6.3.3.5 Reasons for vaccination discontinuation and early study termination

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

6.3.4 Immunogenicity analysis

The primary immunogenicity analysis of the study will be to evaluate the magnitude and breadth of nAb responses and as secondary objective to evaluate immune system activation in individuals with SLE.

6.3.4.1 General approach

For the statistical analysis of immunogenicity endpoints, data from enrolled participants will be used regardless of how many injections they received. Additional analyses may be performed, limited to participants who received all scheduled injections per protocol.

Discrete categorical assay endpoints (eg, response rates) will be analyzed by tabulating the frequency of positive response for each assay by antigen at each timepoint for which an assessment is performed. Crude response rates will be presented with their corresponding 95% confidence interval estimates calculated using the exact method (102).

For quantitative assay data (eg, cytokine quantification by Luminex assay), graphical and tabular summaries of the distributions by antigen, timepoint will be made. Additionally, comparisons to controls selected from other studies may be made by treatment group. For all primary and secondary immunogenicity endpoints, box plots and plots of estimated reverse cumulative distribution curves will be used for graphical display.

6.3.4.2 Primary analyses of neutralization breadth and magnitude

The area-under-the-magnitude-breadth curve (AUC-MB) to a global panel of isolates (103) will be computed for each participant with evaluable neutralization data, as described in (104). Participant-level AUC-MB may also be computed for the historical controls, ideally based on the same global panel of isolates. The 95% CIs about the mean-differences in AUC-MBs between study cohorts will be reported. Regression models may be used to compare the AUC-MB between study cohorts, accounting for potential confounding factors such as age, gender, or other immune responses etc.

The analyses of magnitude-breadth described above are based on the endpoint area-under-the-curve, which is interpreted as the average $\log_{10}$ IC50 to the set of isolates in the test panel. Use of this endpoint is maximally statistically powerful if one study cohort has greater magnitude and breadth than the comparator study cohort, but may miss an effect wherein one study cohort has greater magnitude and the comparator has greater breadth. Therefore, a secondary analysis may compare the distribution of magnitude-breadth curves among cohorts using the

test statistic max$|B_d^G|$ from Huang, et al (104), which is designed to detect general differences in magnitude-breadth curve distributions.

In addition, the geometric mean titers of Nab responses across a panel of isolates will be computed to determine the presence of bnAbs.

6.3.4.3 Analyses of immune activation

Box plots of systemic cytokines, B and T cell populations, and B and T cell activation will be generated for baseline values and for values measured during the course of the study by visit. Each box plot will show the first quartile, the median, and the third quartile. Outliers (values outside the box plot) will also be plotted.

For each assessment of immune activation, summary statistics will be presented by timepoint, as well as changes from baseline for postenrollment values.

6.3.4.4 Multivariate display of immunogenicity endpoints

Data visualization techniques may be used to explore the relationship among immunogenicity readouts. The set of readouts may be based on one of the primary endpoints (eg, nAb), on the set of primary endpoints, or on immunogenicity endpoints that also include secondary or exploratory endpoints. To understand the relationship between pairs of readouts, scatter plots may be used when the number of readouts is small or for a larger number of readouts, a heatmap showing the degree of correlation between any two pairs. Principal component analysis (PCA) and associated 'biplots' of the scores and loadings are particularly useful to understand associations between readouts, especially when readouts are correlated.

6.3.5 Analyses prior to end of scheduled follow-up visits

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

6.3.5.1 Safety

During the course of the trial, safety data will be prepared approximately every 4 months for review by the SMB. Ad hoc safety reports may also be prepared for SMB review at the request of the HVTN 121 PSRT.

6.3.5.2 Immunogenicity analyses

This is an open label vaccine study for which immunogenicity, as measured by neutralization GMT against a standard panel of HIV-1 pseudoviruses, is a primary endpoint of the study. In addition, there are immunogenicity secondary endpoints, and statistical analysis of the secondary immunogenicity endpoint(s) may be performed during the course of the study. Every effort will be made to reduce bias

by not performing early analysis of samples from this study. Where possible, analyses of these secondary endpoints will be performed when all participants have completed the corresponding final immunogenicity visit and data are available for analysis from at least 80% of these participants.

The Laboratory Program will review the analysis report prior to distribution to the protocol chairs, DAIDS, study product developer, and other key HVTN members and investigators. Reports for distribution or presentation should use pubIDs and not PTIDS for individual responses. Distribution of reports will be limited to those with a need to know for the purpose of informing future trial-related decisions. The HVTN leadership must approve any other requests for HVTN immunogenicity analyses prior to the end of the scheduled follow-up visits.

7 Selection and withdrawal of participants

Participants will be low-risk, HIV-uninfected (seronegative) adults, who have been diagnosed with SLE, who comprehend the purpose of the study and have provided written informed consent. Potentially eligible participants will be identified in collaboration with rheumatology clinic(s) and through community advertising, and will then be screened by an initial interview. 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, answers to self-administered and/or interview questions and review of medical records as appropriate.

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 28 days prior to enrollment unless otherwise noted in Sections 7.1 and 7.2.

7.1 Inclusion criteria

General and Demographic Criteria

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

2. **Weight** > 110 pounds

3. Meets **ACR criteria for the classification of SLE** (86, 87, 105) with serologic evidence of disease including a positive test for antinuclear antibodies at a titer of 1:640 or greater, or the presence of a positive test for antibodies to dsDNA, or the presence of anti-Sm, anti-RNP, or anti-Ro antibodies, as documented by medical records and as assessed by a rheumatologist or designee.

4. Currently taking hydroxychloroquine for SLE and for at least 6 months prior to enrollment

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

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

7. **Allows ongoing access to medical records pertaining to their rheumatologic disease**

8. **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

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

HIV-Related Criteria:

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

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

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

Laboratory Inclusion Values

Hemogram/Complete blood count (CBC)

13. **Hemoglobin** ≥ 11.0 g/dL for volunteers who were assigned female sex at birth, ≥ 12.0 g/dL for volunteers who were assigned male sex at birth.

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

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

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

17. **Platelets** = 100,000 to 550,000/mm^3

Chemistry

18. **Chemistry panel**: alanine amino transferase (ALT) and aspartate aminotransferase (AST) < 1.25 times the institutional upper limit of normal; creatinine ≤ institutional upper limit of normal.

Virology

19. **Negative HIV-1 and -2 blood test**: volunteers must have a negative FDA-approved enzyme immunoassay (EIA) within 56 days prior to enrollment.

20. **Negative Hepatitis B surface antigen (HBsAg)** within 56 days prior to enrollment

21. **Negative anti-Hepatitis C virus antibodies (anti-HCV)**, or negative HCV polymerase chain reaction (PCR) if the anti-HCV is positive within 56 days prior to enrollment

Urine

22. **Normal urine by urinalysis**:

    - Negative urine glucose, and
    - Negative or trace urine protein, and
    - Red blood cell (RBC) levels within institutional normal range, and
    - No RBC casts

Reproductive Status

23. **Volunteers who were assigned female sex at birth**: negative serum or urine beta human chorionic gonadotropin (β-HCG) pregnancy test in accordance with local regulatory requirements, performed prior to vaccination on the day of initial vaccination. Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

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

    - Agree to use effective contraception for sexual activity that could lead to pregnancy from at least 21 days prior to enrollment through the last required protocol clinic visit. Effective contraception is defined as using the following methods:
        - Condoms (male or female) with or without a spermicide,
        - Diaphragm or cervical cap with spermicide,
        - Intrauterine device (IUD),
        - Hormonal contraception, or
        - Any other contraceptive method approved by the HVTN 121 PSRT
        - Successful vasectomy in any partner assigned male sex at birth (considered successful if a volunteer reports that a male partner has [1] documentation of azoospermia by microscopy, or [2] a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity postvasectomy);

- Or not be of reproductive potential, such as having reached menopause (no menses for 1 year) or having undergone hysterectomy, bilateral oophorectomy, or tubal ligation;

- Or be sexually abstinent.

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

7.2 Exclusion criteria

General

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

2. **Investigational research agents** not used to treat SLE received within 30 days before first vaccination (additional exclusions may apply, see 13 below)

3. **Intent to participate in another study** of an investigational research agent or any other study that requires non-HVTN HIV antibody testing during the planned duration of the HVTN 121 study

4. **Pregnant or breastfeeding**

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

SLE status. The following criteria must be verified by a rheumatologist or designee

6. **Currently with active lupus** as defined by a Systemic Lupus Erythematosus Disease Activity Index (100) (SELENA-SLEDAI) > 4 (106) (see Appendix G).

7. **Documented SLEDAI score of > 20 in medical record at any time** indicating severe activity (106), or evidence of moderate disease activity (SELENA-SLEDAI > 6) within the last six months, (see Appendix G).

8. **Has had a condition listed on the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)** (105) or has had an increase in the SLICC/ACR D1 score within the last 12 months other than cataracts, premature ovarian failure or diabetes mellitus with approval of the PSRT http://www.clinexprheumatol.org/article.asp?a=2697

9. A history of **central nervous system (CNS) disease**

10. **Thrombotic event within the past 12 months in association with confirmed antiphospholipid antibody**

11. **A history of renal disease** (SLE-related renal injury) confirmed by prior biopsy, active urine sediment, or proteinuria

12. **Prednisone dose** > 10 mg/day for more than 6 months within the past year

13. **Administration of anti-B-cell therapy** (rituximab or belimumab) or any investigational research agents used to treat SLE within the preceding 2 years

14. **Administration of cyclophosphamide** within the preceding year; or administration of mycophenolate mofetil within the last 6 months; or administration of methotrexate, leflunomide, or azathioprine within the last 3 months

15. **Administration of any investigational immunosuppressant medication** within the last year

16. **Administration of other immunosuppressive medications** not listed above, with the exception of topical steroids, topical immunosuppressives (eg, cyclosporine, FK506), or ophthalmic immunosuppressives (eg, steroids, cyclosporine), within 6 months before first vaccination, unless approved by the HVTN 121 PSRT

Vaccines and other Injections

17. **HIV vaccine(s)** received in a prior HIV vaccine trial. For volunteers who have received control/placebo in an HIV vaccine trial, the HVTN 121 PSRT will determine eligibility on a case-by-case basis.

18. **Non-HIV experimental vaccine(s) received within the last 5 years** in a prior vaccine trial. Exceptions may be made by the HVTN 121 PSRT for vaccines that have subsequently undergone licensure by the FDA. For volunteers who have received control/placebo in an experimental vaccine trial, the HVTN 121 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 121 PSRT on a case-by-case basis.

19. **Vaccines** received within 30 days before first study vaccination or scheduled within 30 days after injection (eg, influenza, tetanus, pneumococcal, Hepatitis A or B, measles, mumps, and rubella [MMR]; oral polio vaccine [OPV]; varicella; yellow fever)

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

Immune System

21. **Serious adverse reactions to vaccines or to vaccine components** (such as yeast protein, amorphous aluminum hydroxyphosphate sulfate, L-histidine, polysorbate 80, sodium borate), including history of anaphylaxis and related symptoms such as hives, respiratory difficulty, angioedema, and/or abdominal pain. (Not excluded from participation: a volunteer who had a nonanaphylactic adverse reaction to pertussis vaccine as a child.)

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

23. **Immunodeficiency,** such as common variable immunodeficiency

Clinically significant medical conditions

24. **Ongoing bleeding or hemorrhage** (excluding menstruation), or any subject on anticoagulant therapy

25. **Clinically significant medical condition**, physical examination findings, clinically significant abnormal laboratory results, or past medical history with clinically significant implications for current health, **other than SLE and its manifestations**. 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.

26. **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

27. **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.

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

29. **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.

30. **Uncontrolled diabetes mellitus, Hb A1C > 7.0**. (not excluded: history of isolated gestational diabetes.)

31. **Uncontrolled hypertension**:

    - If a person has a history of hypertension, or is found to have elevated blood pressure or hypertension during screening, 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 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.

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

33. **Malignancy** (not excluded from participation: Volunteer who has had malignancy excised surgically and who, in the investigator's estimation, has a reasonable assurance of sustained cure, or who is unlikely to experience recurrence of malignancy during the period of the study)

34. **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.

35. **Asplenia**: any condition resulting in the absence of a functional spleen (not excluded: splenectomy for splenic trauma)

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

7.3 Participant departure from vaccination schedule or withdrawal

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

7.3.1 Delaying vaccinations for a participant

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

- Within 45 days prior to any study injection
  - Receipt of blood products or immunoglobulin
- Within 30 days prior to any study injection
  - Receipt of other vaccines (eg, influenza, tetanus, pneumococcal, Hepatitis A or B, MMR; OPV; varicella; yellow fever)
  - Receipt of allergy treatment with antigen injections
- Prevaccination abnormal vital signs or clinical symptoms that may mask assessment of vaccine reaction.

Vaccinations should not be administered outside the visit window period specified in the HVTN 121 *Study Specific Procedures*.

In order to avoid vaccination delays and missed vaccinations, participants who plan to receive licensed vaccines or allergy treatments should be counseled to schedule receipt of these substances, when possible, outside the intervals indicated above. The effects of these substances on safety and immunogenicity assessments and their interactions with study vaccines are unknown; for example, reactions to these substances could be misattributed to study product. Therefore, if circumstances allow, these substances should also be avoided in the 30 days after a study vaccination.

7.3.2 Participant departure from vaccination schedule

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

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

However, missed vaccinations may be indicative of medical or social circumstances that indicate the participant should be excluded from future vaccination, and the study team should take this into account when assessing missed vaccinations.

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 121 PSRT)

- Clinically significant condition (ie, a condition that affects the immune system or for which continued vaccinations and/or blood draws may pose additional risk), including but not limited to the following:
  - Pregnancy (regardless of outcome)
  - HIV infection
  - Any grade 4 local or systemic reactogenicity symptom, lab abnormality, or AE that is subsequently considered to be related to vaccination
  - Any grade 3 lab abnormality that is subsequently considered to be related to vaccination
  - Other grade 3 clinical AE that is subsequently considered to be related to vaccination with the exception of fever, vomiting, and subjective local and systemic symptoms. For grade 3 injection site erythema and/or induration, upon review, the HVTN 121 PSRT may allow continuation of vaccination
  - SAE that is subsequently considered to be related to vaccination
  - Clinically significant type 1 hypersensitivity reaction associated with study vaccination. Consultation with the HVTN 121 PSRT is required prior to subsequent vaccinations following any type 1 hypersensitivity reaction associated with study vaccination
  - Related "Severe" SLE flare, as defined by application of the SELENA-SLEDAI instrument (Appendix G)
  - SLE flare is defined clinically by a rheumatologist as severe enough to warrant discontinuation of vaccination
  - New use of mycophenolate mofetil

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

Participants discontinuing study product for reasons other than HIV infection should be counseled on the importance of continuing with the study and strongly encouraged to participate in follow-up visits and protocol-related procedures per the protocol for the remainder of the trial, unless medically contraindicated (see HVTN 121 SSP).

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

7.3.4 Participant termination from the study

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

- Participant refuses further participation,
- Participant relocates and remote follow-up is not possible,
- HVTN CRS determines that the participant is lost to follow-up, or
- Investigator decides, in consultation with Protocol Team leadership, to terminate participation (eg, if participant exhibits inappropriate behavior toward clinic staff).
- Any condition where termination from the study is required by applicable regulations.

8 Study product preparation and administration

CRS pharmacists should consult the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks for standard pharmacy operations. The protocol schema is shown in Table 3-1. See the Investigator's Brochures (IB) for further information about study products.

8.1 Vaccine regimen

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

AIDSVAX® B/E (600 mcg/mL) to be administered as a 1 mL IM injection into the deltoid of the non-dominant arm (unless medically contraindicated) at months 0, 1, and 6.

8.2 Study product formulation

Please refer to the IB for additional information about study product.

AIDSVAX® B/E (labeled as AIDSVAX® B/E **active (MN/A244 rgp 120/HIV-1)** is supplied as a 600mcg/mL sterile suspension in single-use glass vials with a volume to deliver 1 mL consisting of 300 mcg of subtype B (MN) HIV gp120 glycoprotein and 300 mcg of subtype E (A244) HIV gp120 glycoprotein adsorbed onto a total of 600 mcg aluminum as aluminum hydroxide gel suspension as adjuvant. Product is a white to slightly grey suspension with possible product-related particles. Some gel may be visibly adhering to the sides and neck of the vial and should be resuspended using the recommended protocol. The product must be stored upright and kept refrigerated (2° to 8°C). Do not freeze. Do not shake.

8.3 Preparation of study product

8.3.1 AIDSVAX® B/E

One vial of AIDSVAX® B/E will be needed to prepare the dose.

Prior to dispensing, the pharmacist will remove the study product from the refrigerator to allow the vial to equilibrate to room temperature for at least 20 minutes. The pharmacist must then:

1. Gently roll the vial horizontally between the palms or on a hard surface for approximately 10 seconds to wet the interior wall of the vial and to suspend the material.

2. Grasp the vial by the sides. Firmly and forcefully tap the bottom of the vial on a solid surface such that the vial hits squarely on a solid surface, in a rapid series of three (3) taps. Tap with enough force to dislodge any material that may be on the sides of the vial while using care not to chip or break the vial.

3. Repeat the gentle rolling and forceful tapping two more times, resulting in one (1) cycle of 9 taps.

4. Visually inspect the neck of the vial for presence or absence of product-related material (grayish film) as well as the sides of the vial. Vaccine that is stored at 2°C to 8°C can form an appearance of a cloudy ring or 'halo' on the vial neck and/or have product related material adhering on the sidewalls. If either scenario is observed, the pharmacist should continue to follow the steps as directed below to dislodge and uniformly resuspend such product-related material.

5. If residual product-related material still persists at the neck/sides of the vial at the end of the first cycle, repeat steps 1 to 4, for up to two (2) more cycles.

6. If the product-related material is still visible at the end of the third repeated cycle DO NOT use the vial.

After completing these steps, the pharmacist, using aseptic technique, will gently roll the mixture in the vial one more time and then withdraw 1 mL into a 3mL syringe using a 21 or 23 gauge needle.

The syringe should be labeled as "AIDSVAX® B/E 600 mcg." The syringe must also be labeled "for administration into the deltoid of the non-dominant arm." The study product should be administered within 2 hours of being drawn into the syringe.

Any unused portion of entered vials or expired prefilled syringes should be autoclaved immediately prior to disposal and disposed of in accordance with institutional or pharmacy policy. If they will be incinerated, they do not need to be autoclaved.

8.4 Administration

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

For all AIDSVAX B/E injections, the person administering the injection should gently roll the syringe prior to administration of the study product. For these injections, a 21 or 23 gauge needle must be used for administration.

Vaccines will be injected intramuscularly (IM) into the deltoid muscle of the non-dominant arm.

AIDSVAX® B/E will be administered on months 0, 1, and 6.

8.5 Acquisition of study products

AIDSVAX® B/E will be provided by GSID (San Francisco, California, USA).

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

8.6 Pharmacy records

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

8.7 Final disposition of study products

For US clinical research sites, all unused study products must be returned to the CRPMC after the study is completed or terminated unless otherwise instructed by thestudy sponsor. The procedures are included in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.

9 Clinical procedures

The schedule of clinical procedures is shown in Appendix F.

9.1 Informed consent

Informed consent is the process of working with participants so that they fully understand what will and may happen to them while participating in a research study. The HVTN informed consent form (ICF) documents that a participant (1) has been informed about the potential risks, benefits, and alternatives to participation, and (2) is willing to participate in 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 ICFs.

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

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

9.1.1 Screening consent form

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

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

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

9.1.2 Protocol-specific consent forms

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

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

- CRS's IRB/EC and any applicable REs,
- CRS's institution, and
- Elements of informed consent as described in Title 45, CFR Part 46 and Title 21 CFR, Part 50, and in the International Conference on Harmonisation (ICH) E6, GCP: Consolidated Guidance 4.8.

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

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

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

9.1.3 Assessment of Understanding

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

An Assessment of Understanding is used to document the participant's understanding of key concepts in this HIV vaccine trial. The participant must complete the Assessment of Understanding before enrollment. Staff may provide assistance in reading and understanding the questions and responses, if necessary.

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

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

9.2 Pre-enrollment procedures

Screening may occur over the course of several contacts/visits, up to and including before vaccination on day 0. All inclusion and exclusion criteria must be assessed within 28 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, to include medical records review for verification of the diagnosis of SLE where appropriate, and for the presence of any exclusionary medications/conditions;

- 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

- SLE assessment, as determined by a rheumatologist or designee, using standard instruments for this purpose (SELENA-SLEDAI, including Complement profile [C3/C4/CH50] and anti-dsDNA, and SLICC/ACR); and functional status assessment by a staff member using RAPID3;

- Laboratory tests as defined in the inclusion and exclusion criteria, including:
  - Screening HIV test
  - HBsAg
  - Anti-HCV antibodies
  - Syphilis test

  - CBC with differential and platelets
  - Chemistry panel (ALT, AST, and creatinine)
  - Complement Profile (C3/C4/CH50)
  - HbA1C
  - Anti-DNA, Double Stranded (Anti-dsDNA)
  - Urinalysis (as described in section 9.7)
  - Urine or serum pregnancy test (participants who were born female), in accordance with local regulatory requirements

- Administration of behavioral risk assessment questionnaire

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

- Counseling on HIV testing and risk reduction, performed in compliance with the US Centers for Disease Control and Prevention (CDC)'s current guidelines or other local guidelines for HIV counseling, testing, and referral as described in Section 9.5

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

9.3 Enrollment and vaccination visits

Enrollment is simultaneous with first vaccination.

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

- 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;

- CBC/differential/platelets;

- SLE assessment, as determined by a rheumatologist or designee, using standard instruments for this purpose (SELENA-SLEDAI, including Complement profile [C3/C4/CH50] and anti-dsDNA); and functional status assessment by a staff member using RAPID3. Lab results for assessing SLE status must be conducted within 28 days of vaccination and can include using results from a prior visit;

- Assessment of baseline reactogenicity parameters;

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

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

- Serum or urine pregnancy test, in accordance with local regulatory requirements, (for participants who were assigned female sex at birth). Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records) are not required to undergo pregnancy testing;

- Urinalysis (see Section 9.7); and

- Specimen collection (should be completed prior to vaccination)

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

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

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 and9.6); and

- Assessment of new or unresolved social impacts (site staff will ask participant about the status of any unresolved social impacts and if s/he has experienced any new social impacts as a result of the trial participation).

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

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

9.4 Follow-up visits

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

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

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

- Administration of the social impact assessment questionnaire (types of impacts assessed involve personal relationships, health insurance, life insurance, educational or employment opportunities, housing, immigration, or travel);
- HIV infection assessment including pretest counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant;
- Confirm that participants received HIV test results from previous visit. If not, provide test results and post-test counseling as appropriate;
- SLE assessment, as determined by a rheumatologist or designee, using standard instruments for this purpose (SELENA-SLEDAI, including Complement profile [C3/C4/CH50] and anti-dsDNA); and functional status assessment by a staff member using RAPID3;

- CBC/differential/platelets;
- Urinalysis (see Section 9.7);
- Urine or serum pregnancy test (for participants who were assigned female sex at birth), in accordance with local regulatory requirements. Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing; and
- Health contact (see HVTN 121 SSP).

9.5 HIV counseling and testing

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

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

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

Potential participants identified as being HIV-infected during screening are not enrolled. Potential and enrolled participants identified as being HIV-infected will be referred for medical treatment, counseling, and management of the HIV infection. Participants who are found to be HIV-infected after enrollment will not receive any additional study product but will continue to be followed in the study

for safety assessments. These individuals may also be referred to appropriate ongoing clinical trials or observational studies.

9.5.1 Distinguishing intercurrent HIV infection from vaccine-induced positive serology

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

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

- HIV testing will be performed at multiple timepoints throughout the study (see Appendix E). The Laboratory Program (or approved diagnostic laboratory) will follow the HVTN HIV testing algorithm (see *Study Specific Procedures*), 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 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 the end of study will be offered poststudy HIV-1 diagnostic testing (per the HVTN poststudy HIV-1 testing algorithm) periodically and free of charge as medically/socially indicated (approximately every 6 months) unless or until HIV antibody testing is no longer the standard test in clinical settings.

9.5.2 Vaccine-induced seropositivity (VISP) registry

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

contains the names of all study participants, unless they request that their names be removed.

9.6 Contraception status

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

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

9.7 Urinalysis and urine protein:creatinine ratio

A complete urinalysis with microscopy is performed on urine obtained by clean catch. Spot urine protein:creatinine ratio will also be performed.

If the screening urinalysis 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 urinalysis 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 urinalysis is abnormal due to a participant's menstrual period, document in the comment section of the case report form (CRF) and repeat the urinalysis once the participant is no longer menstruating.

9.8 Assessments of reactogenicity

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

The reactogenicity assessment period is 7 full days following each vaccination per the assessment schedule shown in Table 9-1. Participants are instructed to record symptoms using a Participant Diary. Contact between the participant and the site staff should take place at least once within 72 hours/3 days postvaccination. In general, a participant who self-reports any postvaccination reaction greater than mild is seen by a clinician within 48 hours after onset, unless the reaction is improving and/or has completely resolved. Clinic staff will follow new or unresolved reactogenicity symptoms present at day 7 to resolution. Participants are instructed to contact the clinic for events that arise during the period between vaccination and the next scheduled visit.

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

Table 9-1 Schedule of reactogenicity assessments

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

[a] Day of vaccination

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

9.8.1 Assessment of systemic and local symptoms

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

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

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

9.8.2 Assessment of injection site

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

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

9.9 Visit windows and missed visits

Visit windows are defined in HVTN 121 *Study Specific Procedures*. For a visit not performed within the window period, a Missed Visit form is completed. If the missed visit is one that required safety assessments or local safety labs, HVTN CRS staff should attempt to bring the participant in for an interim visit as soon as possible.

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

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

9.10 Early termination visit

In the event of early participant termination, site staff should consider if the following assessments are appropriate: a final physical examination, clinical laboratory tests (including CBC with differential, C3, C4, CH50, anti-dsDNA, urinalysis, spot urine protein:creatinine ratio, and chemistry panel), pregnancy testing, social impact assessment, and HIV test. For participants who have a confirmed diagnosis of HIV infection, see Section 9.12.

9.11 Pregnancy

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

9.12 HIV infection during the study

If a participant becomes HIV-infected during the course of the study, no additional study product will be administered. Participants will be encouraged to continue scheduled study visits for up to 24 weeks following their last study product administration. Follow-up duration for participants diagnosed with HIV infection may be adjusted in consultation with the CRS investigator and the HVTN 121 PSRT (eg, to avoid interference with participant initiation of HIV treatment). At post-infection follow-up visits, only specimens required for protocol-specified safety laboratory tests, urinalysis, spot urine protein:creatinine ratio and pregnancy tests will be collected; in addition, some clinic procedures may be modified or discontinued (see Appendix E and Appendix F).

10 Laboratory procedures

10.1 HVTN CRS laboratory procedures

The HVTN 121 Site Lab Instructions and Study Specific Procedures provide further guidelines for operational issues concerning the clinical and processing laboratories. This document includes guidelines for general specimen collection, special considerations for phlebotomy, specimen labeling, whole blood processing, HIV screening/diagnostic testing, and general screening and safety testing.

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

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

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

10.2 Total blood volume

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

10.3 Primary immunogenicity timepoints

The primary immunogenicity timepoints in this study occur at baseline, 1 week and 2 weeks after the second AIDSVAX vaccination, and 1 week and 2 weeks after the third AIDSVAX vaccination.

Endpoint assays for humoral and cellular responses are performed on specimens collected from participants at the primary immunogenicity timepoints and may be performed at baseline. Depending on the initial results, assays for humoral and cellular responses may be performed on samples collected from participants at other timepoints; the schedule is shown in Appendix E.

It is important to note that the same laboratories that will be running the neutralizing antibody assay and assays for the applicable secondary and exploratory endpoints in HVTN 121 were involved with the non-HVTN studies that will serve as controls (ie, RV328 and CHAVI 005). This will serve to minimize bias when comparing results across groups.

10.4 Endpoint assays: cellular

10.4.1 Intracellular cytokine staining (ICS)

Flow cytometry will be used to examine vaccine-specific CD4+ T-cell responses following stimulation of PBMCs with synthetic HIV peptides that span the proteins encoded by the vaccine. ICS parameters will include cytokines such as interferon gamma (IFN-γ), interleukin (IL)-2, and tumor necrosis factor (TNF)-α, and may include other cytokines (such as cytokines relevant to Th2 and Th17 responses) to identify T cells of specific functionality. Markers of cytotoxic potential (eg, granzyme B) and that identify circulating Tfh cells (eg, CXCR5 and PD-1) may also be included. Data will be reported as percentages of CD4+ T cells responding to a specific peptide pool. Additional cell surface markers, cytokines, or functional markers may also be analyzed.

10.4.2 T and B cell phenotyping

Flow cytometry will be used to phenotype T and B cells in the peripheral blood. Peripheral follicular helper T (pTfh) cells and Treg cells may be characterized based on expression of CXCR5, PD-1, CD127, and CD25 on CD4+ T cells. Additional markers, comprising but not limited to indicators of activation or differentiation may also be included, such as CD21, CD27, CD38, and HLA-DR.

10.5 Endpoint assays: humoral

10.5.1 Neutralizing antibody assay

HIV-1–specific nAb assays will be performed on serum samples from study participants taken at the primary immunogenicity timepoints. The TZM-bl assay will test neutralization of the vaccine strains, a single highly neutralization-sensitive Tier 1 virus as a positive control and the global panel to assess Tier 2 neutralization [125,135]. Additional assays will be performed with viruses that are engineered to detect early precursors of bnAbs. Specimens from other timepoints may also be analyzed at the discretion of the HVTN Laboratory Program, which may be contingent on the results of the primary immunogenicity timepoints.

10.5.2 Binding antibody multiplex assay (BAMA)

HIV-1–specific total binding IgG antibodies will be assessed using serum samples from study participants taken at the primary immunogenicity timepoints and

baseline. In addition, HIV-1–specific total binding IgA antibodies and binding to IgG subclasses (IgG1, IgG2, IgG3, and IgG4) may also be assessed. Specimens from other timepoints may also be assayed based on the results of the initial assay.

10.6 Innate immunity assays

10.6.1 Serum cytokines

Cytokine multiplex assay and/or enzyme-linked immunosorbent assay (ELISA) will be used to measure soluble cytokines, chemokines, and other immunomodulatory factors in the serum. Analytes may include IFN-γ, IL-6, TNF-α, IL-10, IP-10, MCP-1, and/or other analytes may also be included.

10.7 Exploratory studies

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

10.7.1 Antibody-dependent cellular cytotoxicity (ADCC)

ADCC activity may be assessed using serum samples from study participants taken at the primary immunogenicity timepoints. Specimens from the baseline and other timepoints may also be analyzed at the discretion of the HVTN Laboratory Program, which may be contingent on the results of the primary immunogenicity timepoints. For the Granzyme B flow-based cytotoxicity assay, participant sera are incubated with effector cells and gp120-coated target. ADCC is quantified as net percent granzyme B activity which is the percent of target cells positive for GranToxiLux (GTL), an indicator of granzyme B uptake, minus the percent of target cells positive for GTL when incubated with effector cells but without sera. For the Luciferase-based cytotoxicity assay, participant sera are incubated with IMC-infected cells and percent killing is measured through the use of ViviRen luminescence.

10.7.2 BnAb epitope binding and blocking assays

Binding will be assessed using a panel of HIV-1 Env proteins to determine the number and proportion of each type (eg, clade) of Env proteins recognized by participant plasma samples at the primary immunogenicity timepoints and baseline. Blocking will be assessed by the ability of plasma antibody to block the binding of bnAbs to proteins known to bind those bnAbs.

10.7.3 Memory B cell sorts, clonal memory B cell cultures and recombinant antibody production

Memory B cells may be sorted as individual cells for recovery of immunoglobulin genes, sequence analysis, and expression of recombinant mAbs. Genes recovered in this way will be analyzed by comparison to a reference gene set and for inference of the unmutated common ancestor of the antibody, determination of clonal lineage relationships among recovered genes, and compared with genes recovered from other vaccine studies and studies of HIV-1–infected persons. Recombinant mAbs may be assessed for binding, blocking, neutralization, ADCC, and other activities as described for plasma/serum assays.

Blood cell samples taken at timepoints appropriate for memory B cell sorting may also be placed into clonal memory B cell cultures. These cultures will be used to expand the memory B cell populations and supernatants from those cultures may be analyzed for binding, blocking, neutralization, and/or ADCC, or other assays as deemed appropriate. Clonally expanded cells can be immortalized to produce stable cell lines and/or subjected to gene recovery and mAb production.

10.7.4 Plasma cell sorts for B cell repertoire analysis

Blood cell samples taken at timepoints appropriate for plasma cell sorting (~7 days after vaccination) may be sorted to isolate circulating plasmablasts/plasma cells. Cells isolated in this way may have gene isolation and analysis as described in Section 10.7.3.

10.7.5 Next generation sequencing (NGS) for VH and VL

NGS will be performed by reverse transcription and PCR to amplify and sequence variable region gene segments from whole PBMC or isolated B cells from participants. Sequenced gene segments will be aligned to a reference database of variable regions of both heavy and light chain genes to determine gene usage and genetic features of each sequence. This may be performed using paired sequence techniques (eg, by droplet isolation) or on each chain individually.

10.7.6 RNAseq of Tfh and B cell populations

Tfh and B cells will be isolated by flow cytometry either in bulk or as single cells and mRNA isolated. mRNA will be reverse transcribed and complementary DNA (cDNA) amplified for NGS. NGS reads will be aligned to the human reference genome and relative frequency of RNA transcripts in each population will be determined.

10.7.7 Genotyping

Molecular human leukocyte antigen (HLA) typing may be performed on enrolled participants using cryopreserved PBMC collected at baseline, initially on specimens from participants who demonstrate vaccine-induced T-cell responses at

postvaccination timepoints. Other participants (including control recipients) may be HLA-typed to support future studies of immunological interest at the discretion of the HVTN Laboratory Program. Other genes, including those associated with immune responses (eg, immunoglobulin, or T cell receptor genes), or HIV-1 disease progression may also be assessed.

10.8 Specimen storage and other use of specimens

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

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

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

As part of consenting for the study, participants document their initial decision to allow or not allow their specimens to be used in other research, and they may change their decision at any time. The participant's initial decision about other use of their specimens, and any later change to that decision, is recorded by their CRS in a Web-based tool that documents their current decisions for other use of their specimens. The HVTN will only allow other research to be done on specimens from participants who allow such use.

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

10.9 Biohazard containment

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

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

11 Safety monitoring and safety review

11.1 Safety monitoring and oversight

11.1.1 HVTN 121 PSRT

The HVTN 121 PSRT is composed of the following members:

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

The clinician members of HVTN 121 PSRT are responsible for decisions related to participant safety.

The Protocol Team clinic coordinator, clinical data manager, vaccine developer representative, clinical trial manager, and others may also be included in HVTN 121 PSRT meetings.

11.1.2 HVTN SMB

The SMB is a multidisciplinary group consisting of biostatisticians, clinicians, and experts in HIV vaccine research that, collectively, has experience in the conduct and monitoring of vaccine trials. Members of the SMB are not directly affiliated with the protocols under review. An independent rheumatologist will also be available to the SMB to provide expert input on safety concerns related to SLE.

The SMB reviews safety data approximately every 4 months. The reviews consist of evaluation of cumulative reactogenicity events, AE, laboratory safety data, and individual reports of AEs requiring expedited reporting to DAIDS. The SMB conducts additional special reviews at the request of the HVTN 121 PSRT.

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

11.1.3 SDMC roles and responsibilities in safety monitoring

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

- Maintaining a central database management system for HVTN clinical data;
- Providing reports of clinical data to appropriate groups such as the HVTN 121 PSRT and HVTN SMB (see Section 11.1.2);

11.1.4 HVTN Core roles and responsibilities in safety monitoring

- Daily monitoring of clinical data for events that meet the safety pause and HVTN 121 PSRT AE review criteria (see Section 11.3);
- Notifying HVTN CRSs and other groups when safety pauses or planned holds are instituted and lifted (see Section 11.3);
- Querying HVTN CRSs for additional information regarding reported clinical data; and
- Providing support to the HVTN 121 PSRT.

11.2 Safety reporting

11.2.1 Submission of safety forms to SDMC

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

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

11.2.2 AE reporting

An AE is any untoward medical occurrence in a clinical investigation participant administered a study product/procedure(s) and which does not necessarily have a

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

- Unintentional weight loss is required to be reported as an AE only if it is considered to be potentially deleterious to the participant's health (see HVTN 121 *Study Specific Procedures*);

- Injection Site Erythema or Redness and Injection Site Induration or Swelling will not consider interference with usual social and functional activities such that:
  - Grade 1 is: 2.5 to < 5 cm in diameter OR 6.25 to < 25 cm2 surface area;
  - Grade 2 is: ≥ 5 to < 10 cm in diameter OR ≥ 25 to < 100 cm2 surface area;
  - Grade 3 is: ≥ 10 cm in diameter OR ≥ 100 cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage;
  - Grade 4 is: Potentially life-threatening consequences (eg, abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue);

- Non-specific Rash or Skin Changes will be graded using the category of "Skin and subcutaneous tissue disorders – Other, specify" in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, p.140 (Table 11-1):

Table 11-1 Skin and subcutaneous tissue disorders

Skin and subcutaneous disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Skin and subcutaneous tissue disorders – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

- Vasculitis will be graded using the category of "Vascular disorders" in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, p.146 (Table 11-2):

Table 11-2 Vascular disorders

Vascular disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Vasculitis	Asymptomatic; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel					

- Pericarditis will be graded using the category of "Cardiac disorders" in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, p.8 (Table 11-3):

Table 11-3 Cardiac disorders

Cardiac disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pericarditis	Asymptomatic; ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart)					

- Myositis in SLE patients typically presents as muscle weakness, as opposed to pain; thus, myositis will be graded using the parameter of "Neuromuscular Weakness" in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, p.16 (Table 11-4):

Table 11-4 Neurologic adverse events

Neurologic AEs				
	Grade			
Adverse Event	**1**	**2**	**3**	**4**
Neuromuscular Weakness (includes myopathy and neuropathy) *Specify type, if applicable*	Minimal muscle weakness causing no or minimal interference with usual social & functional activities OR No symptoms with decreased strength on examination	Muscle weakness causing greater than minimal interference with usual social & functional activities	Muscle weakness causing inability to perform usual social & functional activities	Disabling muscle weakness causing inability to perform basic self-care functions OR Respiratory muscle weakness impairing ventilation

- Leukopenia in an SLE flare is defined with the SELENA-SLEDAI instrument as a white blood cell count < 3,000 cells/mm^3. The cut point below which an individual is considered to have leukopenia (WBC, Decreased, > 7 days of age) as an AE according to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 is 2,500 cells/mm^3. For the purposes of monitoring this parameter in this study, the cut point for a Grade 1 AE of WBC, Decreased (> 7 days of age) will be <3,000 cells/mm^3, such that study participants with a WBC in the range of 2,000 to 2,999 cells/mm^3 will be considered to have a Grade 1 AE of WBC, Decreased. The grading table applied for WBC, Decreased (> 7 days of age) will therefore be as follows (Table 11-5):

Table 11-5 Lab parameters, hematology

Lab Parameters, Hematology				
	Grade			
Adverse Event	**1**	**2**	**3**	**4**
WBC, Decreased (cells/mm3; cells/L) > 7 days of age	2,000 to 2,999 2.000 x 10^9 to 2.999 x 10^9	1,500 to 1,999 1.500 x 10^9 to 1.999 x 10^9	1,000 to 1,499 1.000 x 10^9 to 1.499 x 10^9	<1,000 <1.000 x 10^9

- Lupus Pleurisy will be graded according to the following table. The components of Pleural Effusion and Pleuritic Pain have been extracted from the category of "Respiratory, thoracic and mediastinal disorders" in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, p.129 (Table 11-6):

Table 11-6 Respiratory, thoracic and mediastinal disorders

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Lupus Pleurisy *Select the highest grade of the following components that are present:* --Pleural Effusion* --Pleural Rub --Pleural Thickening --Pleuritic Pain*	Pleural Effusion: Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Pleural Effusion: Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Pleural Effusion: Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Pleural Effusion: Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
	Pleural Rub	–	–	–	–
	Pleural Thickening	–	–	–	–
	Pleuritic Pain: Mild pain	Pleuritic Pain: Moderate pain; limiting instrumental ADL	Pleuritic Pain: Severe pain; limiting self care ADL	–	–

- Pyuria in an SLE flare is defined with the SELENA/SLEDAI instrument as >5 WBC/high power field. Pyuria is not included in the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 or in the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, November 2017; therefore, pyuria will be graded according to Table 11-7:

Table 11-7 Lab parameters, Urine testing

Lab Parameters, Urine testing				
	Grade			
Adverse Event	**1**	**2**	**3**	**4**
Pyuria	6 to<10 WBCs per high power field	≥10 WBCs per high power field	Gross OR with WBC casts OR intervention indicated	Life-threatening consequences

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 11.3).

Sites are expected to notify HVTN clinical safety staff of any serious safety concern requiring their attention (Table 11-8). Telephone numbers and email addresses are found on the protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn121). Concerns requiring immediate attention should be communicated by calling the clinical safety phone.

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

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

11.2.3 Expedited reporting of AEs to DAIDS

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

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

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

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

The study product for which expedited reporting are required is:

- AIDSVAX® B/E

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).

For additional impact and management of SAEs on the study, see Section 11.3.

11.3 Safety pause and prompt PSRT AE review

When a trial is placed on safety pause, all enrollment and vaccination with the product related to the event that triggered the pause will be held until further notice. The AEs that will lead to a safety pause or prompt HVTN 121 PSRT AE review are summarized in Table 11-8. 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 121 PSRT, participant safety may be threatened. Criteria for an individual participant's departure from the schedule of vaccinations are listed in Section 7.3.

Table 11-8 AE notification and safety pause/AE review rules

Event and relationship to study products	Severity	HVTN CRS action[a]	HVTN Core action
SAE, related	Grade 5 or Grade 4	Phone immediately, email and submit forms immediately	Immediate pause
SAE, not related	Grade 5	Phone immediately, email and submit forms immediately	Immediate PSRT notification
SAE, related	Grade 3, 2, or 1	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause
AE[b], related	Grade 4 or 3	Email and submit forms immediately	Immediate PSRT notification and prompt PSRT AE review to consider pause
"Severe"[c] SLE flare, regardless of relationship	N/A	Phone immediately, email and submit forms immediately	Prompt PSRT AE review
"Mild or moderate"[d,e] SLE flare, related	N/A	Phone immediately, email and submit forms immediately	Prompt PSRT AE review
3 or more confirmed "moderate" or "severe" SLE flares, regardless of relatedness	N/A	Phone immediately, email and submit forms immediately	Immediate pause

[a] Email addresses are found on the Protocol home page on the HVTN Members' site (https://members.hvtn.org/protocols/hvtn121). Phone numbers for each pause rule are in the HVTN 121 SSPs.

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

[c], "Severe" SLE flare is defined by application of the SELENA-SLEDAI instrument (Appendix G).

[d] "Moderate" SLE flare is defined by application of the SELENA -SLEDAI instrument (Appendix G), as well as the determination by a rheumatologist that the participant has flare components/symptoms/lab indices necessitating treatment with a dosage of Prednisone (or equivalent) in the range of >7.5 mg/day to < 0.5 mg/kg/day.

[e] "Mild" SLE flare is defined by application of the SELENA-SLEDAI instrument (Appendix G), as well as the determination by a rheumatologist that the participant has flare components/symptoms/lab indices necessitating treatment with a dosage of Prednisone (or equivalent) of ≤7.5 mg/day.

For all safety pauses, HVTN Core notifies the HVTN 121 PSRT, HVTN Regulatory Affairs, DAIDS Pharmaceutical Affairs Branch (PAB), DAIDS Regulatory Affairs Branch (RAB), DAIDS Safety and Pharmacovigilance Team (SPT), and participating HVTN CRSs. When an immediate safety pause is triggered, HVTN Core notifies the SMB.

Once a trial is paused, the HVTN 121 PSRT reviews safety data and decides whether the pause can be lifted or permanent discontinuation of vaccination is appropriate, consulting the SMB if necessary. HVTN Core notifies the participating HVTN CRSs, HVTN Regulatory Affairs, DAIDS PAB, DAIDS RAB, and DAIDS SPT of the decision regarding resumption or discontinuation of study vaccinations. Based on the HVTN 121 PSRT assessment, DAIDS RAB notifies the FDA as needed.

If an immediate HVTN 121 PSRT notification or prompt HVTN 121 PSRT AE review is triggered, HVTN Core notifies the HVTN 121 PSRT as soon as possible

during working hours (local time)—or, if the information was received during off hours, by the morning of the next work day. If a prompt HVTN 121 PSRT AE review cannot be completed within 72 hours of notification (excluding weekends and US federal holidays), an automatic safety pause occurs.

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

In addition, all other AEs are reviewed routinely by the HVTN 121 PSRT (see Section 11.4.2).

11.4 Review of cumulative safety data

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

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

11.4.1 Daily review

Daily safety reviews are routinely conducted by HVTN Core for events requiring expedited reporting to DAIDS, and events that meet safety pause criteria or prompt HVTN 121 PSRT AE review criteria.

11.4.2 Weekly review

During the injection phase of the trial, the HVTN 121 PSRT reviews clinical safety reports on a weekly basis and conducts calls to review the data as appropriate. After the injections and the final 2-week safety visits are completed, less frequent reporting and safety reviews may be conducted at the discretion of the HVTN 121 PSRT. HVTN Core reviews reports of clinical and laboratory AEs. Events identified during the review that are considered questionable, inconsistent, or unexplained are referred to the HVTN CRS clinic coordinator for verification.

11.5 Study termination

This study may be terminated early by the determination of the HVTN 121 PSRT, a pertinent national regulatory authority, NIH, Office for Human Research Protections (OHRP), the FDA, or study product 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.

12 Protocol conduct

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

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

Any policies or procedures that vary from DAIDS and HVTN standards or require additional instructions (eg, instructions for randomization specific to this study) will be described in the HVTN 121 *Study Specific Procedures.*

12.1 Social impacts

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

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

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

12.2 Emergency communication with study participants

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

When such communication is needed, the CRS will request that its IRB/EC and any applicable RE expedite review of the message. If this review cannot be completed in a timeframe consistent with the urgency of the required communication, the site can contact the participant without IRB/EC approval if such communication is necessary to avoid imminent harm to the study participant. The CRS must notify the IRB/EC and any applicable RE of the matter as soon as possible.

13 Version history

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

The version history of, and modifications to, Protocol HVTN 121 are described below.

Protocol history and modifications

Date: September 12, 2018

Protocol version: 1.02
Protocol modification: Full Protocol Amendment 1

Item 1 Added to the protocol cover page, IND number 018361

Item 2 Revised in Section 9.2, *Pre-enrollment procedures*, the eligibility assessment period from 30 to 28 days to harmonize with Section 7, *Selection and withdrawal of participants*, last paragraph

Item 3 Revised in Section 9.3, *Enrollment and vaccination visit*, SLE assessment and urinalysis

Item 4 Revised in Section 9.4, *Follow-up visits*, Appendix D, *Table of procedures (for sample informed consent form)*, and Appendix F, *Procedures at HVTN CRS,* the timing of when SLE assessments done at some scheduled follow-up visits

Item 5 Added in 11.2.2, *AE reporting*, new guidance to address SLE flare

Item 6 Revised Table 11-1 (now Table 11-8*), AE notification and safety pause/AE review rules*, a new pause rule

Item 7 Updated in Section 13, Version history

Item 8 Corrected cross-referencing errors and updated document URLs

Date: July 12, 2018

Protocol version: 1.0
Protocol modification:

Original protocol

14 Document references (other than literature citations)

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

- Assessment of Understanding. Accessible through the HVTN protocol-specific website.
- Current CDC Guidelines.
- Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. Available at http://www.cdc.gov/mmwr/PDF/rr/rr5514.pdf
- Revised Guidelines for HIV Counseling, Testing, and Referral. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5019a1.htm
- DAIDS Clinical Research Policies and Standard Procedures Documents. Available at https://www.niaid.nih.gov/research/daids-clinical-research-policies-standard-procedures
- DAIDS Protocol Registration Manual. Available at https://www.niaid.nih.gov/sites/default/files/prmanual.pdf
- DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. Corrected Version 2.1, July 2017. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables
- The Manual for Expedited Reporting of Adverse Events to DAIDS. Version 2.0, January 2010. Available at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual
- HVTN Certificate of Confidentiality. Accessible through the HVTN website.
- HVTN 121 Special Instructions. Accessible through the HVTN protocol-specific website.
- HVTN 121 Study Specific Procedures. Accessible through the HVTN protocol-specific website.
- HVTN 121 Site Lab Instructions. Accessible through the HVTN protocol-specific website.
- HVTN Manual of Operations. Accessible through the HVTN website.

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

- Lab assay algorithm (available upon request)

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

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

- NIH *Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules*. Available at http://osp.od.nih.gov/office-biotechnology-activities/biosafety/nih-guidelines

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

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

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

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

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

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

15 Acronyms and abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALT	alanine amino transferase
APS or APLS syndrome	antiphospholipid syndrome or antiphospholipid antibody
ART	antiretroviral therapy
ASIA	autoimmune / inflammatory syndrome induced by adjuvants
AST	aspartate aminotransferase
AUC-MB	area-under-the-magnitude-breadth curve
β-HCG	beta human chorionic gonadotropin
BAMA	binding antibody multiplex assay
bnAb	broadly neutralizing antibody
CAB	Community Advisory Board
CBC	complete blood count
CDC	US Centers for Disease Control and Prevention
cDNA	complementary DNA
CFR	Code of Federal Regulations
CHAVI	Center for HIV-AIDS Vaccine Immunology
CHO cell	Chinese hamster ovary cell
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CRF	case report form
CRPMC	Clinical Research Products Management Center
CRS	clinical research site
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DHHS	US Department of Health and Human Services
dsDNA	double-strand DNA
EAE	adverse events requiring expedited reporting to DAIDS
EC	Ethics Committee
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
FDA	US Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
GCP	Good Clinical Practice
GMT	geometric mean titer
GSID	Global Solutions for Infectious Diseases

GTL	GranToxiLux
HBsAg	hepatitis B surface antigen
HCDR3	heavy chain complementarity determining region 3
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
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	intracellular cytokine staining
IFN-γ	interferon gamma
IL	interleukin
IM	intramuscular
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
mAbs	monoclonal antibodies
MedDRA	Medical Dictionary for Regulatory Activities
MMR	measles, mumps, and rubella
nAb	neutralizing antibody
NAEPP	National Asthma Education and Prevention Program
NGS	next generation sequencing
NIAID	National Institute of Allergy and Infectious Diseases
NIH	US National Institutes of Health (US NIH)
OHRP	US Office for Human Research Protections
OPV	oral polio vaccine
PAB	Pharmaceutical Affairs Branch
PBMC	peripheral blood mononuclear cell
PCA	principal component analysis
PCR	polymerase chain reaction
PSRT	Protocol Safety Review Team
pTfh	peripheral follicular helper T
qPCR	quantitative polymerase chain reaction
RAB	Regulatory Affairs Branch
RAPID3	Routine Assessment of Patient Index Data 3
RE	regulatory entity
RSC	Regulatory Support Center

SAE	serious adverse event
SCHARP	Statistical Center for HIV/AIDS Research and Prevention
SDMC	statistical and data management center
SELENA Assessment	Safety of Estrogens in Lupus Erythematosus National
SICF	sample informed consent form
SLE	systemic lupus erythematosus
SLEDAI	SLE Disease Activity Index
SLICC/ACR DI	Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index
SMB	Safety Monitoring Board
SPT	DAIDS Safety and Pharmacovigilance Team
SSA	Sjögren's syndrome A
TB	tuberculosis
Tfh	T follicular helper
TNF-α	tumor necrosis factor alpha
Treg	T regulatory
UW-VSL	University of Washington Virology Specialty Laboratory
VISP	Vaccine induced seropositivity
WBC	white blood cells

16 Literature cited

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Appendix A Sample informed consent form (SICF)

Title: A phase 1b open label clinical trial to evaluate HIV-1 neutralization antibody breadth in response to HIV gp120 protein vaccine in HIV-uninfected adults with quiescent Systemic Lupus Erythematosus

HVTN protocol number: HVTN 121

Site: [Insert site name]

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

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

About the study

The HIV Vaccine Trials Network (HVTN) and [Insert site name] are doing a study to test an HIV vaccine given to people who have Systemic Lupus Erythematosus (SLE). Some people may just call this "Lupus." HIV is the virus that causes AIDS. Vaccines against HIV are designed to teach the body to produce antibodies against HIV. Antibodies are one of the body's natural ways of protecting against infections.

People who have Lupus may have immune responses that are unique. The responses might be different from people who do not have Lupus. One of these responses is the body's ability to develop antibodies in response to infections.

Special antibodies called broadly neutralizing antibodies (bnAbs) are able to protect against many different types of an infection, such as the different types of HIV found around the world. Because bnAbs are an important focus of HIV vaccine research, researchers would like to understand more about this immune response in people who have Lupus. They want to better understand how the bnAb responses differ from people who do not have Lupus.

About 16 people will take part in this study at multiple sites. The researcher in charge of this study at this clinic is [Insert name of site PI]. The US National Institutes of Health (NIH) is paying for the study.

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

   - How do the immune systems of people with Lupus respond to the study vaccine? (Your immune system protects you from disease.)

- Do the immune systems of people with Lupus make bnAbs in response to the study vaccine?

- Is the study vaccine safe to give to people without active symptoms of Lupus?

- Are people with Lupus able to take the study vaccine without becoming too uncomfortable?

2. The study vaccine cannot give you HIV.

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

3. The study vaccine likely will not change your risk of becoming infected with HIV if you are exposed to the virus.

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

The vaccine has been given to thousands of people in other studies. In those studies, most people were not protected from infection with HIV. It's very important to avoid exposure to HIV during and after the study. We will tell you how to avoid HIV.

4. This study vaccine is experimental.

The study vaccine is called AIDSVAX® B/E. From here on, we will call it the study vaccine. It is an experimental HIV vaccine. This vaccine is used only in research studies.

The vaccine is being provided by Global Solutions for Infectious Diseases (GSID). The AIDSVAX® B/E vaccine is made of man-made proteins that are similar to proteins from the outer surface of the HIV virus. The vaccine is also made with an adjuvant called aluminum hydroxide. An adjuvant is something added to the vaccine to help the immune system respond better. Aluminum hydroxide adjuvants are used in many licensed vaccines that have been given to millions of people. Your body's immune system may respond to this study vaccine by making antibodies that recognize and fight against HIV proteins. Antibodies are special proteins made by the body that can recognize and prevent infections. The AIDSVAX® B/E vaccine has been given to over 10,000 participants in different studies with people who do not have Lupus.

General risks of vaccines:

Generally, vaccinations are considered safe for people with inactive Lupus.

All vaccines can cause fever, chills, rash, aches and pains, nausea, headache, dizziness, and feeling tired. Vaccines can also cause pain, redness, swelling, or

itching where you got the injection. Most people can still do their planned activities after getting a vaccine. Rarely, people have side effects that limit their normal activities or make them go to the doctor.

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

Very rarely, a vaccine causes an autoimmune disease in a person, or makes an autoimmune disease worse. An autoimmune disease happens when your immune system attacks your own body, instead of attacking an infection. You already have one autoimmune disease, Lupus. We do not know if getting the study vaccine could put you at risk for getting additional autoimmune diseases.

We do not know if getting the study vaccine could impact your Lupus, causing it to flare up. If you have a significant lupus flare up, we will stop your vaccinations and continue to check on your health. We will work with your doctor to get you the care you need.

Risks of the study vaccine:

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

This AIDSVAX® B/E vaccine has been given to thousands of people who do not have Lupus. The most common symptoms at the injection site were pain and tenderness. In some cases, this resulted in some limited arm movement which went away on its own within a few days. Less often, some people had injection site hardness. The most common reactions in the body were headaches, swollen glands, and muscle or joint aches. Some people also reported feeling weak or having low energy.

A few people had changes in blood and urine test results following injections. We do not know if these changes were caused by the study vaccine. The changes did not cause health problems.

One person experienced a serious allergic reaction immediately after a vaccination with AIDSVAX® B/E. The person was treated and recovered completely in a few hours.

We do not know if participants with Lupus in this study will have similar side effects to those seen in earlier studies with participants who did not have Lupus. Also, people with Lupus may have different side effects.

Joining the study

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

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

   If you join this study, you may not be allowed to join other HIV vaccine or HIV prevention studies now or in the future. You cannot be in this study while you are in another study where you get a study product. Being in more than one study may not be safe.

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

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

Site: Remove item 6 if you use a separate screening consent that covers these procedures.

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

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

   - Checking your weight, temperature and blood pressure
   - Looking in your mouth and throat
   - Listening to your heart and lungs
   - Feeling your abdomen (stomach and liver)

   We will also do blood and urine tests. These tests tell us about some aspects of your health, such as how healthy your kidneys, liver, and immune system are, and if you have diabetes. We will also test you for: Syphilis, Hepatitis B, and Hepatitis C. We will ask you about medications you are taking. We will ask you about behaviors that might put you at risk for getting HIV. If you were assigned female sex at birth, we will test you for pregnancy.

   We will assess your Lupus status to see if you have any currently active symptoms. This includes blood tests, a physical exam, and a questionnaire.

   We may need to review your medical records. We will ask for your permission if this is needed.

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

Site: Adapt the following section so it is applicable to the care available at your site

7. **If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here.**

   For the care that we cannot give, we will explain how we will help you get care elsewhere. For health problems that are unrelated to the study, we will not pay for care.

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

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

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

Being in the study

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

9. **You will come to the clinic for scheduled visits about [#] times over 12 months.**

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

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

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

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

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

Payments you receive for being in the study may be taxable. We may need to ask you for your Social Security number for tax reasons.

You do not have to pay anything to be in this study. The study vaccine, the medical visits, and laboratory tests related to this study will be covered by the clinic, through the study sponsor. However, routine medical care (care you would have received whether or not you were in this study) will be charged to you or your insurance company. You may wish to contact your insurance company to discuss this further.

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

You will get 3 injections during the study by injection into the muscle of your upper arm.

Injection schedule		
First vaccination visit	1 month	6 months
AIDSVAX® B/E	AIDSVAX® B/E	AIDSVAX® B/E

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

12. In addition to giving you the study product, we will:

- Do regular HIV testing, as well as counseling on your results and on how to avoid getting HIV
- Do physical exams
- Do pregnancy tests if you were assigned female sex at birth
- Ask questions about your health, including medications you may be taking
- Ask questions about any personal problems or benefits you may have from being in the study
- Assess your Lupus status

- Take urine and blood samples.

When we take blood, the amount will depend on the lab tests we need to do. It will be some amount between 15 mL and 315 mL (1 tablespoon to 1½ cups). Your body will make new blood to replace the blood we take out.

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

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

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

It is important that you contact the clinic if you have any symptoms between your vaccination and the next scheduled visit. If you think you are having a flare up, please contact the clinic as soon as possible.

13. We will counsel you on avoiding HIV infection.

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

14. The HVTN will test your samples to see how your immune system responds to the study product.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Researchers may also do genetic testing on your samples.

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

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

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

People who may see your information are:

- Researchers who use your extra samples and information for other research
- Government agencies that fund or monitor the research using your extra samples and information
- The researcher's Institutional Review Board or Ethics Committee
- Any regulatory agency that reviews clinical trials

- The people who work with the researcher

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

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

Site: Check Health Insurance Portability and Accountability Act (HIPAA) authorization for conflicts with this section.

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

Site: Any change to the following boxed text requires approval from HVTN Regulatory Affairs. You can remove the box around the text.

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

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

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

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

- The US National Institutes of Health (NIH) and its study monitors,
- The US Food and Drug Administration (FDA),
- Any regulatory agency that reviews clinical trials
- [Insert name of local IRB/EC] ,

- [Insert name of local and/or national regulatory authority as appropriate],
- Global Solutions for Infectious Diseases (GSID) and people who work for them,
- The HVTN and people who work for them,
- The HVTN Safety Monitoring Board, and
- The US Office for Human Research Protections (OHRP).

All reviewers will take steps to keep your records private.

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

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

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

Site: Include the following boxed text. You can remove the box around the text.

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

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

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

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

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

This may happen if:

- you do not follow instructions,
- we think that staying in the study might harm you,
- you have more than a mild Lupus flare,
- you enroll in a different research study where you get another study product, or
- the study is stopped for any reason.

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

18. We will stop your injections if you become pregnant.

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

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

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

We will encourage you to stay in the study for up to 24 weeks if you choose. We will discuss your study options with you. We will counsel you about your HIV infection and about telling your partner(s). We will tell you where you can get support and medical care. *Site: Modify the following sentence as appropriate.* We will not provide or pay for any of your HIV care directly.

Other Risks

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

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

Risks of routine medical procedures:

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

Personal problems/discrimination/testing HIV antibody positive:

About 10 to 20% of people who join HVTN studies report personal problems or discrimination because of joining an HIV vaccine study. Family or friends may worry, get upset or angry, or assume that you are infected with HIV or at high risk and treat you unfairly as a result. Rarely, a person has lost a job because the study took too much time away from work, or because their employer thought they had HIV.

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

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

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

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

If you become pregnant during or after the study and have VISP, we don't know if the antibodies could be passed to your baby. We know that this happens with

other vaccines, like tetanus vaccine. These antibodies from the mother are not a danger to the baby, and they go away over time. For most babies antibodies from the mother last for about six months.

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

Embarrassment/anxiety:

You may feel embarrassed when we ask about your HIV risks, such as having sex and using drugs. Also, waiting for your HIV test results or other health test results could make you feel anxious. You could feel worried if your test results show that you are infected with HIV. If you feel embarrassed or anxious, please tell us and we will try to help you.

Risks of disclosure of your personal information:

We will take several steps to protect your personal information. Although the risk is very low, it is possible that your personal information could be given to someone who should not have it. If that happened, you could face discrimination, stress, and embarrassment. We can tell you more about how we will protect your personal information if you would like it.

Risks of genetic testing:

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

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

Unknown risks:

We do not know if the study vaccine will increase, decrease, or not change your risk of becoming infected with HIV if exposed. If you get infected with HIV, we

do not know how the study vaccine might affect your HIV infection or how long it takes to develop AIDS.

We do not know if getting this study vaccine will affect how you respond to any future approved HIV vaccine. 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

21. The study may not benefit you.

We do not expect that the study vaccine will benefit you in any way. We do not know if there will be benefit from this research for the larger community of people who have Lupus. 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. The information learned in this study will help to inform the larger field of HIV vaccine research. However, if the study vaccine later becomes approved and sold, there are no plans to share any money with you.

Your rights and responsibilities

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

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

Leaving the study

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

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

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

Injuries

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

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

Your health is important to us. *(Site: Adjust the following 2 sentences if applicable to the care available at your site)* We will tell you about the care that we can give here. For the care that we cannot provide, we will help you get care elsewhere by referring you for treatment.

If you become sick or injured in this study, please tell your study doctor. There are no funds to pay for treatment of study-related injuries or Lupus flares (regardless of whether or not they are study related). Your insurance company may not be willing to pay for study-related injury or for Lupus flares that occur while you are in the study. If you have no insurance, you would be responsible for any costs.

Questions

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

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

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

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

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

Your permissions and signature

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

26. In Section 14 of this form, we told you about possible other uses of your extra samples and information, outside this study. Please choose only one of the

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

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

OR

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

OR

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

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

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

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

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

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

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

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

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

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

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

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

You must agree to use effective birth control from 21 days before your first injection until after your last required protocol clinic visit.

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

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

You do not have to use birth control if:

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

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

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

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

Title: A phase 1b open label clinical trial to evaluate HIV-1 neutralization antibody breadth in response to HIV gp120 protein vaccine in HIV-uninfected adults with quiescent Systemic Lupus Erythematosus

HVTN protocol number: HVTN 121

Site: [Insert site name]

When samples are no longer needed for this study, the HVTN wants to use them in other studies and share them with other researchers. The HVTN calls these samples "extra samples." The HVTN will only allow your extra samples to be used in other studies if you agree to this. You will mark your decision at the end of this form. If you have any questions, please ask.

1. Do I have to agree?

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

2. Where are the samples stored?

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

3. How long will the samples be stored?

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

4. Will I be paid for the use of my samples?

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

5. Will I benefit from allowing my samples to be used in other studies?

Probably not. Results from these other studies are not given to you, this clinic, or your doctor. They are not part of your medical record. The studies are only being done for research purposes.

6. Will the HVTN sell my samples and information?

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

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

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

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

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

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

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

Researchers may also do genetic testing on your samples.

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

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

10. What are the risks of genetic testing?

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

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

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

People who may see your information are:

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

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

Questions

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

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

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

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

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

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

OR

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

OR

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

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

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

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

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

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

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

			Time after 1st injection visit											
Procedure	Screening visit(s)	First injection visit	1 week	2 weeks	1 month	5 weeks	6 weeks	3 months	6 months	6 ¼ months	6.5 months	7.5 months[2]	8.5 months	12 months
Injection		√			√				√					
Medical history	√													
Complete physical	√	√	√	√	√	√	√	√	√	√	√		√	√
Urine test	√	√	√	√	√	√	√	√	√	√	√		√	
Blood drawn	√	√	√	√	√	√	√	√	√	√	√		√	√
Pregnancy test (participants assigned female sex at birth)[1]	√	√			√				√					
HIV testing and pretest counseling	√						√				√			√
Risk reduction counseling	√	√	√	√	√	√	√	√	√	√	√		√	√
SLE status assessment	√	√	√	√	√	√	√	√	√	√	√		√	
Interview/ questionnaire	√	√	√	√	√	√	√	√	√	√	√		√	√
Health assessment contact												√		

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

[2]Clinic staff and study participants will be in contact to collect information about their health.

Appendix E Laboratory procedures

					Tube volume (mL)															
				Visit:	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**[11]	**13**	**14**	
				Day:	Screening	D0	D7	D14	D28	D35	D42	D84	D168	D175	D182	D210	D238	D364	
				Month:	visit[3]	M0	M0.25	M0.5	M1	M1.25	M1.5	M3	M6	M6.25	M6.5	M7.5	M8.5	M12	
						AIDSVAX B/E			**AIDSVAX B/E**				**AIDSVAX B/E**						
Procedure	**Ship to**[1]	**Assay Location**[2]	**Tube**[4]	**Tube size (vol. capacity)**[4]																**Total**
BLOOD COLLECTION																				
Screening or diagnostic assays																				
Screening HIV test	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—		5
HBsAg/anti-HCV	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—		5
Syphilis	Local Lab	Local Lab	SST	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—		5
HIV diagnostics[9]	UW-VSL	UW-VSL	EDTA	10mL	—	—	—	—	—	—	10	—	—	—	10	—	—	20[9]		40
Safety labs[12]																				
Hb A1C	Local lab	Local lab	EDTA	5mL	5	—	—	—	—	—	—	—	—	—	—	—	—	—		5
CBC/ Diff/ platelets	Local lab	Local lab	EDTA	5mL	5	5	5	5	5	5	5	5	5	5	5	—	5	—		60
Chemistry panel[5]	Local lab	Local lab	SST	5mL	5	—	—	5	—	—	5	5	—	—	5	—	5	—		30
Complement profile C3/C4/CH50	Local lab	Local lab	SST	5mL	5	5	5	5	5	5	5	5	5	5	5	—	5	—		60
Anti-dsDNA	Local lab	Local lab	SST	5mL	5	5	5	5	5	5	5	5	5	5	5	—	5	—		60
Immunogenicity assays[6]																				
Host genetics[7]	CSR	HVTN Labs	ACD	8.5mL	—	17	—	—	—	—	—	—	—	—	—	—	—	—		17
Cellular assays																				
ICS	CSR	HVTN Labs	ACD	8.5mL	—	25.5	—	—	—	**—**	—	—	—	**—**	***25.5***	—	—	25.5		76.5
T and B cell phenotyping	CSR	HVTN Labs	ACD	8.5mL	—	34	—	—	—	***42.5***	17	—	42.5	***42.5***	34	—	—	34		246.5
Memory B cell sorts and recombinant Ab production	CSR	Non-HVTN Labs at Duke-DHVI	ACD	8.5mL	—	—	—	—	—	—	25.5	—	—	—	***25.5***	—	—	51		102
Plasma cell sorts for B cell repertoire analysis	CSR	Non-HVTN Labs at Duke-DHVI	ACD	8.5mL	—	—	—	—	—	—	—	—	—	***25.5***	—	—	—	—		25.5
Humoral assays																				
Binding Ab	CSR	HVTN Labs	SST	8.5mL	—	8.5	—	—	—	—	***8.5***	—	8.5	—	***8.5***	—	—	8.5		42.5
Neutralizing Ab	CSR	HVTN Labs	SST	8.5mL	—	***8.5***	—	—	—	—	***8.5***	—	8.5	—	***8.5***	—	—	8.5		42.5
ADCC	CSR	HVTN Labs	SST	8.5mL	—	y	—	—	—	—	y	—	y	—	y	—	—	y		0
bnAb epitope binding and blocking assays	CSR	Non-HVTN Labs at Duke-DHVI	ACD	8.5mL	—	z	—	—	—	z	z	—	z	z	z	—	—	z		0
Innate immunity																				
Serum cytokines	CSR	HVTN Labs	SST	5mL	—	5	—	—	—	***5***	5	—	5	***5***	5	—	—	5		35
Sequencing																				
Next generation sequencing for VH and VL	CSR	Non-HVTN Labs at Duke-DHVI	ACD	8.5mL	—	25.5	—	—	—	—	25.5	—	—	25.5	25.5	—	—	25.5		127.5
RNAseq of Tfh and B cell populations	CSR	Non-HVTN Labs at Duke-DHVI	ACD	8.5mL	—	25.5	—	—	—	—	25.5	—	—	25.5	25.5	—	—	25.5		127.5
Specimen storage																				
PBMC	CSR		ACD	8.5mL	127.5	17	—	—	—	—	—	—	17	42.5	17	—	—	85		306
Plasma	CSR		ACD	8.5mL	z	z	—	—	—	z	z	—	z	z	z	—	—	z		0
Serum	CSR		SST	8.5mL	17	—	—	—	—	—	—	—	—	—	—	—	—	8.5		25.5
Visit total					**185**	**182**	**15**	**20**	**15**	**63**	**146**	**20**	**97**	**182**	**205**	**0**	**20**	**297**		**1444**
56-Day total					**185**	**366**	**381**	**401**	**416**	**479**	**480**	**243**	**97**	**278**	**483**	**483**	**225**	**297**		
URINE COLLECTION[12]																				
Urinalysis with microscopy[10]	Local lab	Local lab			X	X	X	X	X	X	X	X	X	X	X	—	X	—		
Spot urine protein:creatinine ratio	Local lab	Local lab			X	X	X	X	X	X	X	X	X	X	X	—	X	—		
Pregnancy test[8]	Local lab	Local lab			X	X	—	—	X	—	—	—	X	—	—	—	—	—		

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

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

Non-HVTN laboratory: Duke Human Vaccine Institute (Durham, North Carolina, USA).

[3] Screening may occur over the course of several contacts/visits up to and including before vaccination on day 0. Storage specimens should be drawn no later than Day -15.

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

[5] Chemistry panels are defined in Section 9.2 (pre-enrollment) and Section 9.4 (Follow-up visits).

[6] Immunogenicity assays will be performed at M0, M1.25, M1.5, M6.25, and M6.5. Based on the number of responders observed at these timepoints, lab assays may be performed on participants for humoral and cellular responses at other timepoints.

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

[8] For a participant who was born female (ie, assigned female sex at birth), pregnancy test must be performed on urine or blood specimens within 24 hours of vaccination with negative results received prior to vaccination. Persons who have undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing.

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

[10] Urinalysis with microscopy is defined in Sections 7.1, 9.2, and 9.7.

[11] For information concerning the visit 12 health assessment contact, see Section 9.4 and HVTN 121 SSP.

[12] For participants with confirmed diagnosis of HIV infection, only specimens required for protocol-specified safety laboratory tests, urinalysis, spot urine protein:creatinine ratio, and pregnancy tests will be collected.

y = SST collected for binding Ab and neutralizing Ab assays will also cover specimen needs for ADCC; no separate blood draw is needed.

z = Up to 10 x 1mL aliquots of ACD plasma will be harvested during PBMC processing; no separate blood draw is needed.

Appendix F Procedures at HVTN CRS

Visit:	**01**[1]	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**
Day:		D0	D7	D14	D28	D35	D42	D84	D168	D175	D182	D210	D238	D364
Month:		M0	M0.25	M0.5	M1	M1.25	M1.5	M3	M6	M6.25	M6.5	M7.5	M8.5	M12
Procedure	Scr.	VAC1			VAC2				VAC3					
Study procedures[2]														
Signed screening consent (if used)	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Assessment of understanding	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Signed protocol consent	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Medical history	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Complete physical exam	X	X	X	X	X	X	X	X	X	X	X	—	X	X
Risk reduction counseling[3]	X	X	X	X	X	X	X	X	X	X	X	—	X	X
Pregnancy prevention assessment[4]	X	X	X	X	X	X	X	X	X	X	X	—	X	X
Behavioral risk assessment[5]	X	—	—	—	—	—	—	X	X	—	—	—	X	X
Confirm eligibility, obtain demographics	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Social impact assessment	—	X	X	X	X	X	X	X	X	X	X	—	X	X
Social impact assessment questionnaire	—	—	—	—	—	—	—	X	X	—	—	—	—	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	—	X	X
Intercurrent illness/adverse experience	—	X	X	X	X	X	X	X	X	X	X	—	X	X
HIV infection assessment[6]	X	—	—	—	—	—	X	—	—	—	X	—	—	X
Confirm HIV test results provided to participant	—	X	—	—	—	—	—	X	—	—	—	—	X	—
SLE status assessment/functional assessment[7]	X	X	X	X	X	X	X	X	X	X	X	—	X	—
Health assessment contact[8]	—	—	—	—	—	—	—	—	—	—	—	X	—	—
Local lab assessment[9]														
Urinalysis and spot urine protein;creatinine ratio	X	X	X	X	X	X	X	X	X	X	X	—	X	—

Visit:	**01**[1]	**02**	**03**	**04**	**05**	**06**	**07**	**08**	**09**	**10**	**11**	**12**	**13**	**14**
Day:		D0	D7	D14	D28	D35	D42	D84	D168	D175	D182	D210	D238	D364
Month:		M0	M0.25	M0.5	M1	M1.25	M1.5	M3	M6	M6.25	M6.5	M7.5	M8.5	M12
Procedure	Scr.	VAC1			VAC2				VAC3					
Pregnancy (urine or serum HCG)[10]	X	X	—	—	X	—	—	—	X	—	—	—	—	—
CBC, differential/platelets	X	X	X	X	X	X	X	X	X	X	X	—	X	—
Chemistry panel (see Section 9.2)	X	—	—	X	—	—	X	X	—	—	X	—	X	—
Syphilis, Hepatitis B, Hepatitis C	X	—	—	—	—	—	—	—	—	—	—	—	—	—
Complement profile (C3/C4/CH50)	X	X	X	X	X	X	X	X	X	X	X	—	X	—
Anti-dsDNA	X	X	X	X	X	X	X	X	X	X	X	—	X	—
Vaccination procedures[11]														
Vaccination[12]	—	X	—	—	X	—	—	—	X	—	—	—	—	—
Reactogenicity assessments[13]	—	X	—	—	X	—	—	—	X	—	—	—	—	—

[1] Enrollment and screening visits can occur on the same day

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

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

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

[5] Not applicable to HIV-infected participants.

[6] Includes pre-test counseling and HIV testing. A subsequent follow-up contact is conducted to provide post-test counseling and to report results to participant. If a participant has a confirmed diagnosis of HIV infection, do not perform HIV infection assessment.

[7] SELENA-SLEDAI, RAPID3. SLICC/ACR at screening only.

[8] CRS staff and study participants will be in contact to collect information about their health (see HVTN 121 SSP).

[9] For participants with a confirmed diagnosis of HIV infection, only specimens listed under “Safety labs,” urinalysis, spot urine protein:creatinine ratio, and pregnancy tests specified in Appendix E will be collected.

[10] For a participant who was assigned female sex at birth, pregnancy test must be performed on the day of vaccination prior to vaccination. Pregnancy test to determine initial eligibility may be performed at screening, but must also be done on day 0 prior to first vaccination. Persons who are NOT of reproductive potential due to having undergone total hysterectomy or bilateral oophorectomy (verified by medical records), are not required to undergo pregnancy testing. Serum pregnancy tests may be used to confirm the results of, or substitute for, a urine pregnancy test, in accordance with local regulatory requirements.

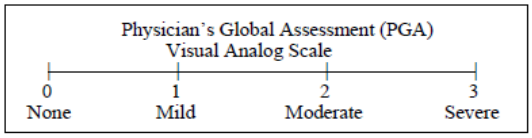
[11] Not applicable to HIV-infected participants.

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

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

Appendix G SELENA-SLEDAI Instrument

SELENA-SLEDAI Flare Composite



SELENA-SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) INSTRUMENT SCORE

Check box: if descriptor is present at the time of visit or in the preceding 10 days.

Wt	Check if Present	Descriptor	Definition
8	☐	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.
8	☐	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.
8	☐	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intellectual function, with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐	Visual disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. Exclude hypertension, infection or drug causes.
8	☐	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	☐	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	☐	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	☐	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	☐	Urinary casts	Heme-granular or red blood cell casts.
4	☐	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	☐	Proteinuria	New onset or recent increase of more than 0.5 gm/24 hours.
4	☐	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	☐	Rash	Ongoing inflammatory lupus rash.
2	☐	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	☐	Mucosal ulcers	Ongoing oral or nasal ulcerations due to active lupus.
2	☐	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	☐	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	☐	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	☐	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	☐	Fever	>38°C. Exclude infectious cause.
1	☐	Thrombocytopenia	<100,000 platelets/mm^3.
1	☐	Leukopenia	<3,000 white blood cells/mm^3. Exclude drug causes.

_____ **TOTAL SCORE** (Sum of weights next to descriptors marked present)

Categorize as "Mild or Moderate" Flare or "Severe" Flare if the patient has at least one of the listed criteria in that category:	
Mild or Moderate Flare ☐	**Severe Flare** ☐
☐ Increase in SLEDAI ≥ 3 points, but not > 12	☐ Increase to a SLEDAI > 12
☐ New/worse: • Discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus • Nasopharyngeal ulcers • Pleuritis • Pericarditis • Arthritis • Fever (SLE)	☐ New/worse: • CNS-SLE • Vasculitis • Nephritis • Myositis • Platelet count < 60,000 (equivalent to 60 x 10^9/L) • Hemolytic anemia: Hemoglobin <7.0 g/dL or decrease in Hemoglobin >3.0 g/dL Requiring a doubling of prednisone dose, or prednisone increase to >0.5 mg/kg/day, and/or hospitalization
☐ Increase in prednisone, but not to >0.5 mg/kg/day	☐ Increase in prednisone to >0.5 mg/kg/day
☐ Added NSAID or Plaquenil (hydroxychloroquine) for SLE activity	☐ New Cytoxan (cyclophosphamide), Azathioprine, Methotrexate for SLE activity ☐ Hospitalization for SLE activity
☐ ≥1.0 Increase in Physician's Global Assessment (PGA) score, but not to more than 2.5	☐ Increase in Physician's Global Assessment (PGA) score to > 2.5

Appendix H HVTN low risk guidelines for the US

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

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

1. Sexual behaviors

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

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

AND

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

In the **last 6 months**:

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

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

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

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

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

AND

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

2. Non-sexual behaviors

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

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

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

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

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

Appendix I Protocol signature page

A phase 1b open label clinical trial to evaluate HIV-1 neutralization antibody breadth in response to HIV gp120 protein vaccine in HIV-uninfected adults with quiescent Systemic Lupus Erythematosus

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

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

DAIDS Protocol Number: HVTN 121

DAIDS Protocol Version: 2.0

Protocol Date: September 14, 2018