Clinical Research Protocol

SAFETY, IMMUNOGENICITY AND ANTI-RESERVOIR ACTIVITY OF AN ELECTROPORATION-ADMINISTERED HIV DNA VACCINE ENCODING GAG, POL AND ENV PROTEINS WITH IL-12 PLASMID IN HIV-INFECTED ADULTS ON ANTIRETROVIRAL THERAPY

Protocol Number:	DAIDS-ES 38409
Version Date:	Version 2.1
Investigational Product:	Human Immunodeficiency Type 1 DNA Plasmid (gag, pol, env; E.coli; VGXI, Inc.; PENNVAX®-GP) Vaccine, with IL-12 DNA Plasmid (expressing p35 and p40 genes; E.coli; VGXI, Inc.) as Adjuvant, with Electroporation Device (Cellectra®; Inovio)
IND Number:	17795
Development Phase:	Phase I/IIA
Sponsor:	University of California, San Francisco
Funding Organization:	NIAID/NIH
Principal Investigator:	Steven G. Deeks
Coordinating Center:	UCSF Data Coordinating Center

Approval:

PI or Sponsor Signature (Name and Title)

1/11/18

Date

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Protocol Signature Page

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

Signature of Investigator of Record **Date (Month/Day/Year)**

Investigator of Record (PRINT NAME)

Full Protocol Title: Safety, immunogenicity and anti-reservoir activity of an electroporation-administered HIV DNA vaccine encoding Gag, Pol and Env proteins with IL-12 plasmid in HIV-infected adults on antiretroviral therapy

DAIDS Protocol Number: 38409

DAIDS Protocol Version: 2.1

Protocol Date: January 11, 2018

LIST OF ABBREVIATIONS

ADDC	Antibody-dependent cellular cytotoxicity (ADCC)
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
ART	Antiretroviral therapy
ATI	Analytic treatment interruption
CRF	Case report form
CRP	C-reactive protein
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
IM	Intramuscular
IV	Intravenous
PI	Principal Investigator
PK	Pharmacokinetic
PRD	Participant Reminder Diary
SAE	Serious adverse event

PROTOCOL SYNOPSIS

TITLE	Safety, immunogenicity and anti-reservoir activity of an electroporation-administered HIV DNA vaccine encoding Gag, Pol and Env proteins with IL-12 plasmid in HIV-infected adults on antiretroviral therapy
SPONSOR	University of California, San Francisco
PRINCIPLE INVESTIGATOR	Steven G. Deeks, MD
FUNDING ORGANIZATION	NIAID/NIH
NUMBER OF SITES	Two (UCSF and UCLA)
RATIONALE	Durable control of HIV in the absence of antiretroviral therapy (a "remission") will likely require potent and sustained HIV-specific CD8+ T cells that target conserved epitopes. VGX-3100 is an HPV DNA vaccine that generates sustained T cell responses which are able to traffic to an immunosuppressive tissue environment and clear virus-expressing target cells. Remarkably, 49.5% of vaccinees exhibited histopathologic regression of cervical intraepithelial neoplasia (as compared to 30% of placebo-recipients, P=0.03). A closely related electroporation (EP)-delivered HIV DNA vaccine (PENNVAX) has been studied for prevention and is known to be both safe and highly immunogenic. The therapeutic potential of this approach in HIV disease remains unknown and will be the focus of this study. The mechanisms which account for immune clearance and control of the HIV reservoir are not known. Based on observations made in "elite" controllers, clearance of HIV during ART and control of HIV post-ART will likely require the generation of sustained HIV-specific CD8+ T cells that target conserved regions and have potent cytotoxic and proliferative capacity. No therapeutic vaccine has yet demonstrated this capacity. Most vaccines developed specifically for cure research do not include the highly variable *env* gene or Env proteins for this reason; indeed, it is commonly assumed that the inclusion of this highly immunogenic region blunts immunologic response to more conserved regions and is hence detrimental. More recent data from studies of HIV prevention, elite controllers and so-called "post-treatment" controllers have argued that non-neutralizing Env-specific antibodies capable of stimulating antibody-dependent cellular cytotoxicity (ADCC) by recruiting NK cells and other effector responses may also be critical, suggesting that any effective therapeutic vaccine will need to generate responses to this protein. To date, there has been no randomized study evaluating the impact of Env antigens in a therapeutic setting.

STUDY DESIGN	Cohort A: Randomized, double-blinded, placebo-controlled assessment of EP-delivered DNA vaccine targeting consensus multiclade HIV Gag/Pol antigens versus Gag/Pol/Env antigens (each administered with IL-12 DNA adjuvant) in HIV-infected adults who initiated ART during chronic infection. Cohort B: A single-arm study of the DNA vaccine targeting Gag/Pol/Env (with IL-12 DNA) in HIV-infected adults who initiated ART during acute HIV infection will also be performed.
PRIMARY OBJECTIVE	To determine the safety and tolerability of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease. To determine the immunogenicity of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease.
SECONDARY OBJECTIVES	To determine the anti-reservoir activity of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease.
NUMBER OF SUBJECTS	Cohort A, Randomized placebo-controlled clinical study of EP-administered *gag/pol/IL-12*, EP-administered *gag/pol/env/IL-12* and matching placebo in HIV-infected adults for whom ART was initiated during chronic infection: 15 per arm (45 subjects) Cohort B, Single arm study of EP-administered *gag/pol/env/IL-12* DNA plasmids in HIV-infected adults for whom ART was initiated during hyperacute and acute HIV infection: 15 subjects
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1 Willing and able to provide written informed consent 2 Male or female, age ≥ 18 and ≤ 65 years 3 HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load. 4 For Cohort A participants, ART initiated during chronic infection (e.g., more than 6 months after estimated date of infection, or as determined by site investigator and/or available medical records). 5 For Cohort B participants, ART initiated during “hyperacute” HIV infection (Fiebig I/II) or early HIV infection (Fiebig III/IV).

6 On continuous antiretroviral therapy for at least 24 months without any interruptions of greater than 14 consecutive days, and on a stable regimen for at least 8 weeks, without plans to modify ART during the study period

7 Screening plasma HIV RNA levels < 40 copies/mL on all available determinations in past 24 months (isolated single values ≥ 40 but < 200 copies/mL will be allowed if they were preceded and followed by undetectable viral load determinations)

8 Screening CD4+ T-cell count ≥ 350 cells/mm^3

9 Creatinine Clearance (CrCl) > 60 mL/min via Cockroft-Gault method at screening

10 The following laboratory criteria must be met at screening:

- Absolute neutrophil count (ANC) ≥ 1000 neutrophils/mm^3
- Hemoglobin ≥ 10.0 g/dL
- Platelet count ≥ 100,000/uL
- Aspartate aminotransferase (AST) ≤ 2x upper limit of normal (ULN)
- Alanine aminotransferase (ALT) ≤ 2x ULN

<u>Exclusion Criteria</u>:

11 Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study

12 Active malignancy requiring systemic chemotherapy or surgery in the preceding 3 months or for whom such therapies are expected in the subsequent 6 months

13 Active (untreated) HCV or HBV infection

14 Decompensated liver disease as defined by the presence of ascites, encephalopathy, esophageal or gastric varices, or persistent jaundice

15 Serious illness requiring systemic treatment and/or hospitalization in the 3 months prior to study enrollment

16 Concurrent treatment with immunomodulatory drugs, and/or exposure to any immunomodulatory drug in the 4 weeks prior to study enrollment (e.g. corticosteroid therapy equal to or exceeding a dose of 15 mg/day of prednisone for more than 10 days, IL-2, interferon-alpha, methotrexate, cancer

	chemotherapy). NOTE: use of inhaled or nasal steroid is not exclusionary. 17 Serious medical or psychiatric illness that, in the opinion of the site investigator, would interfere with the ability to adhere to study requirements or to give informed consent. 18 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements or to give informed consent. 19 Unable to undergo leukapheresis procedure 20 Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0; 21 Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles; 22 Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site; 23 Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist); 24 Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	PENNVAX®-GP and INO-6145 are circular, double stranded, deoxyribonucleic acid consisting of synthetic plasmids that encode multi-clade consensus sequences from *gag/pol* and *env* genes (PENNVAX®-GP) or *gag/pol* only (INO-6145). HIV plasmids are co-administered with an IL-12 plasmid by intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA® 2000.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Study products will be administered at Day 0 and Weeks 4, 8 and 12. Subjects will be observed on study for up to 64 weeks.
CONCOMITANT MEDICATIONS	No restrictions will be placed on the antiretroviral drug regimen. All subjects should be maintained on the same medications throughout the entire study period, as medically feasible.
EFFICACY EVALUATIONS	Using standard and innovative measures of immunogenicity, we will determine the capacity of our vaccine strategies to stimulate broad, functional T cell responses against novel HIV epitopes, and comprehensively characterize the impact of the vaccine on several innate and adaptive immune parameters. The size of the active and

	latent reservoirs before, during and after vaccination will be measured.
PRIMARY ENDPOINTS	• Safety and tolerability • The magnitude and breadth of T cell responses will be evaluated by the IFN-γ enzyme-linked immunospot (ELISpot) assay. The breadth of Gag-specific responses will be characterized in detail via matrix mapping, while pools of 15 overlapping peptides will used to evaluate responses to Pol, Env and Nef (internal control).
SECONDARY ENDPOINTS	• Frequency of circulating CD4+ T cells harboring replication-competent HIV as measured using multiplex digital droplet PCR assay to quantify the *total* number of intact proviruses.
OTHER EVALUATIONS	• Magnitude of T cell responses to the most frequent potential T cell epitopes (PTE) for Env, Gag, Pol and Nef. • Polyfunctionality and cytotoxic capacity will be assessed by evaluating Gag-specific CD4+ and CD8+ T cell production of cytokines (IFN-γ, TNF-α, IL-2) and the cytotoxic molecules perforin and granzyme B • Phenotypic characteristics (e.g., PD-1, TIGIT, CD160, 2B4, Tbet, Eomesodermin, IRF4) of longitudinally studied pre-existing and *de novo* vaccine-induced HIV-specific CD8+ T cell populations (as detected using MHC class I-specific tetramers) • Functional features of HIV-specific antibodies (ADCC, phagocytosis, complement-mediated destruction, neutrophil activation, and dendritic cell uptake) • Transcriptomic analysis of FACS sorted tetramer-detectable populations using RNASeq methods • Plasma HIV RNA (single copy assay), cell-associated RNA, cell-associated DNA
SAFETY EVALUATIONS	All subjects will be followed for possible adverse events (AEs) throughout their involvement in the study. Routine blood work will be performed on a regular basis. AEs will be graded according to Corrected Version 2.1 (July 2017) of the NIH/NIAID Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.
PLANNED INTERIM ANALYSES	A Safety Monitoring Committee (SMC) will be convened and will meet biannually to review all adverse events and the conduct of the study. Serious adverse events will be monitored by the committee on an ongoing basis throughout the study.

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1 BACKGROUND

Although antiretroviral therapy (ART) decreases HIV-associated mortality, it does not appear to completely restore health, for reasons that remain unclear. In addition, while prevention approaches have seen some significant successes in the past few years, the epidemic continues to grow both locally and globally. Perhaps the only way to fully address these and other limitations is to effectively eradicate HIV from infected persons. While complete eradication may never be feasible, a "functional cure" in which patients are able to maintain undetectable viral loads indefinitely in the absence of therapy may be possible. The best evidence for this is the existence of "elite controllers" and more recently individuals treated during very early HIV infection ("post-treatment controllers").

Our program is based on the premise that durable remission in HIV disease will require generating a potent and sustained virus-specific CD8+ T cell response that is able to continuously clear and/or suppress virus-producing cells that arise from reactivation of the latent pool. Previous efforts to boost CD8+ T cell immunity in a therapeutic setting have largely failed, in part because the effector responses in vaccinated individuals were weak, transient, and targeted immunodominant epitopes that often have already escaped[1,2]. Given the dissemination of the viral reservoir and the rapid rate of virus spread during a treatment interruption, it is likely that the virus overwhelmed any vaccine-mediated T cell responses.

Historical efforts aimed at "auto-vaccinating" HIV infected individuals with their own virus via scheduled treatment interruptions, aimed at priming more effective immunity and ultimate control of viremia, resulted in relatively disappointing results[3]. This failure is likely due to three major barriers. First, pre-existing immune exhaustion within the HIV-specific CD8+ T cell population may have hampered the induction of *de novo* highly effective responses. Second, exposure to autologous virus may have simply recalled immunity to highly immunodominant responses that had already failed due to the selection for escape mutations. Third, the number of effector cells able to contain a robust rebounding virus population may have been insufficient, thus allowing the virus to outpace the immune response ("too little, too late").

Our program is inspired by recent successes of a human papillomavirus (HPV) therapeutic vaccine (VGX-3100) delivered by electroporation (EP). In a randomized clinical trial of 167 women with pre-malignant cervical disease, VGX-3100 - a DNA vaccine that targets HPV-16/18 proteins - generated a potent and sustained CD8+ T cell response[4]. These cells were able to traffic to an immunosuppressive tissue environment and clear virus-expressing target cells. Remarkably, 49.5% of vaccinees exhibited histopathologic regression (as compared to 30% of placebo-recipients, P=0.03). To our knowledge, no prior therapeutic vaccine targeting a chronic viral infection in humans has achieved anything close to this outcome. A closely related EP-delivered HIV DNA vaccine (PENNVAX) has been studied for prevention and is known to be both safe and highly immunogenic[5]. The therapeutic potential of this approach in HIV disease remains unknown, although a pilot study recently confirmed that the vaccine is safe and immunogenic in treated HIV disease[6].

1.1 Overview of PENNVAX-GP

PENNVAX®-GP is an admixture of SynCon® INO-6112 (*env* A/ *env* C) with SynCon® INO-6145 (*Mpol*/*gag*). SynCon® INO-6112 consists of 2 plasmids encoding for synthetic consensus clade A and C HIV-1 Envelope proteins. This combination of SynCon antigens drive cytotoxic T

lymphocytes (CTL) against B clade as well. SynCon® INO-6145 consists of 2 plasmids containing synthetic HIV-1 multiclade (A, B, C and D) consensus *pol*, and *gag*. The *IL-12* DNA adjuvant (INO-9012) consists of a single plasmid containing a dual promoter system for expression of both the IL-12 p35 and p40 genes necessary for production of the active heterodimeric (p70) IL-12 protein.

2 STUDY RATIONALE

2.1 Study Rationale and Hypothesis

Millions of HIV-infected individuals are now receiving life-saving antiretroviral therapy.[7] However, mortality remains high, particularly in resource-limited countries.[8] Moreover, chronic HIV-infected individuals demonstrate persistent immune activation despite ART-mediated viral suppression, which is an independent predictor of mortality in this setting.[9] Given the current absence of an effective HIV vaccine, finding a cure for HIV will likely have a large impact on the long-term health of ART-treated HIV-infected individuals, in particular for those living in resource-limited settings.

Based on these studies, we predict that exposure to a highly immunogenic heterologous DNA vaccine with an IL-12 adjuvant will generate robust CD8+ T cell responses against novel epitopes. Theoretically, having an "army" of such cells that are primed and ready to rapidly respond to an exponentially expanded virus population will be needed after ART is interrupted and at the time of virus rebound if the immune system is to get ahead of the virus and maintain its control.

We additionally hypothesize that there will be differences in the HIV-specific T cell responses generated in vaccine recipients who initiated ART during acute HIV infection (Fiebig I-II and III-IV) compared to those who initiated ART during chronic HIV infection, due to presumed greater global immune function and fewer T-cell escape mutants in the viral reservoir with earlier initiation of ART. We expect potentially more functional and effective T cell responses, as well as differences in gag epitope responses, whether an increase in breadth of response or shift in responses to different epitopes.

2.2 Risk / Benefit Assessment

There is no expected direct benefit for the study participant. The primary benefit is the gain in knowledge regarding a potentially effective intervention that may in future studies allow for a durable control of HIV in absence of therapy (a remission). The risk of participating in this study is minimal. The vaccine and the IL-12 adjuvant have been extensively studied in the past. The only known adverse events are local reactions, which are mild and transient. There is only a limited theoretical risk for significant adverse events.

2.3 Program Overview

The central premise of our program is that durable control of HIV in the absence of antiretroviral therapy ("remission") will require the generation of *de novo* potent and sustained HIV-specific CD8+ T cell responses that target evolutionarily conserved epitopes. Our program is inspired by the recent success of VGX-3100 (Inovio), a DNA therapeutic vaccine for HPV that leads to histopathologic regression of pre-malignant lesions in people and is associated with a potent, sustained boost to HPV-specific CD8+ T cell populations. A closely related *gag/pol/env* DNA vaccine administered with an *IL-12* DNA plasmid (PENNVAX-B, Inovio) has been studied for HIV prevention and is known to be both safe and highly immunogenic. The therapeutic potential of this novel approach is unknown and will be the focus of our work in this protocol. In a randomized placebo-controlled study we will compare the immunogenicity and anti-reservoir activities of *gag/pol* DNA versus *gag/pol/env* DNA (both administered with IL-12). We will determine for the first time in established HIV disease whether presence of *env* in a DNA

vaccine blunts T cell responses to more conserved Gag-specific and Pol-specific epitopes. We will also determine if Env-specific responses (which will presumably be mediated by antibodies and ADCC) have a measurable effect on reservoir. Our study will leverage the considerable strengths of our established multi-disciplinary research team to pursue highly innovative approaches to measuring vaccine immunogenicity and the viral reservoir.

3 STUDY OBJECTIVES

3.1 Primary Objectives

- To determine the safety and tolerability of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease.
- To determine the immunogenicity of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease.

3.2 Secondary Objective

- To determine the anti-reservoir activity of EP-administered *gag/pol/IL-12* or *gag/pol/env/IL-12* DNA plasmids in treated HIV disease.

4 STUDY DESIGN

4.1 Study Overview

Cohort A. We will perform a three-arm, randomized, double-blinded, placebo-controlled assessment of HIV DNA vaccine with IL-12 in 45 HIV-infected adults for whom ART was initiated during chronic infection. Participants will be randomized 1:1:1 to each of three arms:

- Placebo administered by IM/EP at Day 0 and Weeks 4, 8 and 12
- *gag/pol* and *IL-12* plasmids administered by IM/EP at Day 0 and Weeks 4, 8 and 12
- *gag/pol, env* and *IL-12* plasmids administered by IM/EP at Day 0 and Weeks 4, 8 and 12

Participants will be screened for eligibility. Individuals meeting inclusion criteria without meeting exclusion criteria will be enrolled in the study and randomized to one of three arms. Enrollment of participants in Cohort A with CD4+ T cell count nadir of <200 cells/mm^3 will be capped at 50%. Participants will receive vaccine/IL-12 or placebo by electroporation at weeks 0, 4, 8 and 12.

Cohort B. A single arm study of EP-administered *gag/pol/env/IL-12* DNA plasmids will also be performed in 15 HIV-infected adults for whom ART was initiated during hyperacute and acute HIV infection. We will seek to enroll 7-8 participants who initiated ART during Fiebig stages I-II and 7-8 participants who initiated ART during Fiebig stages III-IV. All participants will receive *Gag/Pol, Env* and *IL-12* plasmids administered by IM/EP at Day 0 and Weeks 4, 8 and 12. Randomization will not be performed for Cohort B as the sample size of 15 would not provide adequate power to compare between arms and feasibility is low to enroll a larger cohort of individuals who initiated ART during acute HIV infection. The primary comparison for Cohort B will be to Cohort A, gag/pol/env/IL-12 arm.

The primary and secondary endpoints will be safety, immunogenicity and anti-reservoir activity. The total duration of the study is expected to be 64 weeks.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoints

- Safety and tolerability
- The magnitude and breadth of T cell responses will be evaluated by the IFN-γ enzyme-linked immunospot (ELISpot) assay. The breadth of Gag-specific responses will be characterized in detail via matrix mapping, while pools of 15 overlapping peptides will used to evaluate responses to Pol, Env and Nef (internal control).

5.2 Secondary Endpoint

- Frequency of circulating CD4+ T cells harboring replication-competent HIV as measured using multiplex digital droplet PCR assay to quantify the total number of intact proviruses.

5.3 Other Endpoints

- Magnitude of T cell responses to the most frequent potential T cell epitopes (PTE) for Env, Gag, Pol and Nef.
- Polyfunctionality and cytotoxic capacity will be assessed by evaluating Gag-specific CD4+ and CD8+ T cell production of cytokines (IFN-γ, TNF-α, IL-2) and the cytotoxic molecules Perforin and Granzyme B
- Phenotypic characteristics (e.g., PD-1, TIGIT, CD160, 2B4, Tbet, Eomesodermin, IRF4) of longitudinally studied pre-existing and de novo vaccine-induced HIV-specific CD8+ T cell populations (as detected using MHC class I-specific tetramers)
- Functional features of HIV-specific antibodies (ADCC, phagocytosis, complement-mediated destruction, neutrophil activation, and dendritic cell uptake)
- Transcriptomic analysis of FACS sorted tetramer-detectable populations using RNASeq methods
- Plasma HIV RNA (single copy assay)
- Cell-associated RNA
- Cell-associated DNA

6 SUBJECT SELECTION

6.1 Study Population

Subjects with HIV infection who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Willing and able to provide written informed consent
2. Male or female, age ≥ 18 and ≤ 65 years
3. HIV-1 infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry and confirmed by a licensed Western blot or a second antibody test by a method other than the initial rapid HIV and/or E/CIA, or by HIV-1 antigen or plasma HIV-1 RNA viral load.
4. For Cohort A participants, ART initiated during chronic infection (e.g., more than 6 months after estimated date of infection, or as determined by site investigator and/or available medical records).
5. For Cohort B participants, ART initiated during "hyperacute" HIV infection (Fiebig I/II) or early HIV infection (Fiebig III/IV).
6. On continuous antiretroviral therapy for at least 24 months without any interruptions of greater than 14 consecutive days, and on a stable regimen for at least 8 weeks, without plans to modify ART during the study period
7. Screening plasma HIV RNA levels < 40 copies/mL on all available determinations in past 24 months (isolated single values ≥ 40 but < 200 copies/mL will be allowed if they were preceded and followed by undetectable viral load determinations)
8. Screening CD4+ T-cell count ≥ 350 cells/mm^3
9. Creatinine Clearance (CrCl) > 60 mL/min via Cockroft-Gault method at screening
10. The following laboratory criteria must be met at screening:
    - Absolute neutrophil count (ANC) ≥ 1000 neutrophils/mm^3
    - Hemoglobin ≥ 10.0 g/dL
    - Platelet count ≥ 100,000/uL
    - Aspartate aminotransferase (AST) ≤ 2x upper limit of normal (ULN)
    - Alanine aminotransferase (ALT) ≤ 2x ULN

6.3 Exclusion Criteria

1. Pregnant, breastfeeding, or unwilling to practice birth control during participation in the study
    a. Acceptable birth control is defined as the following:

i. For female participants of childbearing potential, two of the following forms of contraception are required, one of which must be a barrier method:

1. Condoms (male of female) with or without a spermicidal agent
2. Diaphragm or cervical cap with spermicide
3. Intrauterine device (IUD) with published data showing that expected failure rate is < 1% per year
4. Tubal ligation
5. Hormone-based contraceptive such as oral birth control pills

ii. Male participants participating in sexual activity that could lead to pregnancy must agree to at least one reliable method of contraception of the above listed

2. Active malignancy requiring systemic chemotherapy or surgery in the preceding 3 months or for whom such therapies are expected in the subsequent 6 months
3. Active (untreated) HCV or HBV infection
4. Decompensated liver disease as defined by the presence of ascites, encephalopathy, esophageal or gastric varices, or persistent jaundice
5. Serious illness requiring systemic treatment and/or hospitalization in the 3 months prior to study enrollment
6. Concurrent treatment with immunomodulatory drugs, and/or exposure to any immunomodulatory drug in the 4 weeks prior to study enrollment (e.g. corticosteroid therapy equal to or exceeding a dose of 15 mg/day of prednisone for more than 10 days, IL-2, interferon-alpha, methotrexate, cancer chemotherapy). NOTE: use of inhaled or nasal steroid is not exclusionary.
7. Serious medical or psychiatric illness that, in the opinion of the site investigator, would interfere with the ability to adhere to study requirements or to give informed consent.
8. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements or to give informed consent.
9. Unable to undergo leukapheresis procedure
10. Acute or chronic bleeding or clotting disorder that would contraindicate IM injections or use of blood thinners (e.g. anticoagulants or antiplatelet drugs) within 2 weeks of Day 0;
11. Less than two acceptable sites available for IM injection considering the deltoid and anterolateral quadriceps muscles;
12. Tattoos, keloids or hypertrophic scars located within 2 cm of intended treatment site;
13. Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located in ipsilateral deltoid injection site (unless deemed acceptable by a cardiologist);
14. Metal implants or implantable medical device within the intended treatment site (i.e. electroporation area);

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible.

Subjects must provide their own antiretroviral drugs. No restrictions will be placed on the antiretroviral drug combinations. If medically feasible, study participants will be encouraged to remain on their entry antiretroviral regimen through week 64 of the study.

Participation in the study will not interfere in any manner with the subject's standard of care.

Given the potential immune-modifying activities of the vaccine and IL-12 adjuvants, other immunodulatory drugs (e.g., cytokines, systemic corticosteroids, most biologics) will be discouraged if medically feasible.

Routine or standard of care vaccinations (such as influenza, pneumococcal, and meningococcal vaccinations) are allowed but must be administered greater than 14 days prior to baseline leukapheresis and first (Day 0) protocol-administered vaccination and greater than 14 days prior to each of the week 14 and week 48 visits.

8 STUDY TREATMENTS

8.1 PENNVAX®-GP and IL-12 Expression Plasmids

PENNVAX®-GP is a circular, double stranded, deoxyribonucleic acid consisting of expression plasmids that encode synthetic HIV-1 multiclade consensus Gag, Pol and Env proteins. INO-6145 is a circular, double stranded, deoxyribonucleic acid consisting of expression plasmids that encode synthetic HIV-1 multiclade consensus Gag and Pol proteins. The IL-12 DNA adjuvant (INO-9012) consists of a single plasmid containing a dual promoter system for expression of both the *IL-12 p35* and *p40* genes necessary for production of the active heterodimeric (p70) IL-12 protein.STUDY Procedures

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

Blood collection will occur at all visits and will be timed to stay within Red Cross Guidelines (less than 500 mL every 8 weeks).

SCOPE questionnaires will be administered for data collection and clinical assessments as described in Sections 9.1-9.3.

8.2 Concomitant Medications

All concomitant medications taken within 30 days prior to screening and entry and a complete history of ART, HIV-1 related vaccines, and immune-based therapies will be documented at the Screening and Entry visits.

At each subsequent visit, all additions or discontinuations of prescription medications should be recorded. Actual or estimated start and stop dates should be recorded.

8.3 Demographics and Medical History

Demographic information (date of birth, sex, race and ethnicity) will be recorded at Screening.

At Screening, the first Baseline visit (B1) and Entry (Day 0), the medical history must include all diagnoses within the past 30 days and, regardless of when the diagnosis was made, a complete history of chronic conditions, malignancies, and AIDS-defining conditions. Self-reported or documented nadir CD4+ T cell count should be recorded.

Any allergies to any medications or their formulations should also be recorded.

8.4 Clinical Assessment

Signs and Symptoms

At pre-entry (leukapheresis), all grades of signs and symptoms that occurred 30 days prior to the visit must be recorded.

At entry and all post-entry visits, all grades of signs and symptoms that occurred since the previous visit must be recorded. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF). Criteria for participant management, dose interruptions, modifications, and discontinuation of treatment will be mandated only for toxicities attributable to the study medication(s).

Diagnoses

All clinical events and new diagnoses or changes in diagnoses should be recorded.

Subject Self Evaluation

Subjects will be provided a Participant Reminder Diary (PRD, as shown in Appendix 1) and will be asked to record the following the evening of study treatment through Day 6:

- General symptoms of feeling unwell
- Pain and itching at injection site
- Measure redness, swelling, bruising at injection site
- Medications taken

The completed PRD will be reviewed with the subject by the study staff at the next in-person visit.

The study staff will review the PRD for general symptoms (e.g. malaise, fatigue, headache, nausea, and myalgia/arthralgia), injection site reaction symptoms (e.g. pain, erythema and edema), medical events and medications. All reported events will be assessed for clinical significance (CS) and reported as adverse events accordingly in the CRF.

8.5 Physical Examination

Complete Physical Exam

A complete physical examination should be conducted at screening. It is to include at minimum an examination of the skin, head, mouth, and neck, auscultation of the chest, cardiac and abdominal exam, examination of the lower extremities for edema, and Karnofsky performance score. The complete physical exam will also include resting vital signs (temperature, pulse, respiratory rate, and blood pressure), height and weight.

Targeted Physical Exam

A targeted physical examination should be conducted at each subsequent visit following screening. It is to include resting vital signs (temperature, pulse, respiratory rate, blood pressure) and weight, and is to be driven by any new signs or symptoms that the participant has experienced since the last visit.

8.6 Clinical Laboratory Measurements

Hematology

Complete blood count (hemoglobin, hematocrit, red blood cell count, white blood cell count, white blood cell differential, and platelet count) will be obtained at screening, the first baseline visit (B1), entry, and all post-entry visits.

Chemistry

Serum sodium, potassium, chloride, bicarbonate, random glucose, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), alkaline phosphatase, total bilirubin, and albumin will be obtained at screening, entry, and all post-entry visits except week 64. Serum calcium will also be obtained at screening and Week 12.

Pregnancy Testing

A serum or urine β-human chorionic gonadotropin HCG test (urine test must have a sensitivity of 25 mIU/mL) will be obtained from female subjects with reproductive potential at screening and prior to each dosing visit (Day 0, Weeks 4, 8, and 12).

8.7 HIV Clinical Laboratory Measures

Blood will be obtained and sent to a CLIA-certified or equivalent laboratory for real-time determination of absolute CD4+ and CD8+ T cell counts, percentages, and CD4/CD8 ratio and plasma HIV-1 RNA quantification (viral load) at Screening, B1, Entry, and Weeks 4, 14, 24, 36, 48, 64, and premature discontinuation visits. All efforts should be made to have collection of blood for T cell counts occur between 8am and 11am, in order to account for diurnal variation in CD4+ T cell count.

8.8 Cryopreservation of Plasma

Plasma will be collected and stored at the indicated visits.

8.9 Cryopreservation of PBMCs

PBMCs will be collected and stored at the indicated visits.

8.10 Collection of PAXgene specimen

Whole blood will be collected in PAXgene tubes at the indicated visits.

8.11 Pharmacokinetic Measurements

No pharmocokinetic studies are planned for this study.

8.12 Immunologic Measures

T cell immunogenicity. T cell immunogenicity will be measured via several different assays, with laboratory personnel and those involved in raw data analysis blinded with regards to participant study arm and study time point. A comprehensive analysis of baseline peripheral blood T cell responses will be compared to newly-generated T cell responses detectable in PBMCs at the peak of the vaccine response (week 14 of the study, 2 weeks after the last dose of vaccine or placebo) to determine how the vaccine impacts the magnitude, breadth, phenotype and function of HIV-specific CD4+ and CD8+ T cell responses. In addition to this comparison (baseline versus peak), ELISpot assays will be performed on PBMCs from the memory time point (week 48) to determine the magnitude and breadth of persistent vaccine-induced responses.

Our main immunogenicity outcome will be to characterize the magnitude and breadth of T cell responses to therapeutic vaccination using the IFN-γ enzyme-linked immunospot (ELISpot) assay. The magnitude and breadth of Gag-specific responses will be characterized in detail via matrix mapping using vaccine-matched peptides, while pools of 15 overlapping peptides will used to evaluate the magnitude of T cell response to Pol and Env, as well as Nef (internal control). In addition, ELISpot responses to pools of Gag, Pol, Env, and Nef peptides (n=50 peptides/pool) that have been derived from circulating HIV viruses (potential T cell epitope peptides, PTE; NIH AIDS Reagent Program) will be evaluated in parallel. All measures will be performed on two baseline PBMC samples.

Polyfunctionality and cytotoxic phenotype will be assessed by evaluating Gag-specific CD4+ and CD8+ T cell production of cytokines (IFN-γ, TNF-α, IL-2) and the cytotoxic molecules Perforin and Granzyme B, as well as degranulation (as evidenced by upregulation of CD107a) after short-term *in vitro* peptide stimulation[6].

Tetramer analysis of exhaustion phenotype. One of the major goals of HIV therapeutic vaccination is to determine whether it is possible to induce functional HIV-specific CD8+ T cell responses that are not exhausted. At the baseline and peak time points, we will characterize in more depth the phenotype and transcriptional state of existing and vaccine-elicited HIV-specific CD8+ T cell responses using MHC Class I tetramers. We will identify and follow longitudinally pre-existing and *de novo* vaccine-induced HIV-specific CD8+ T cell populations before and after vaccination, and characterize CD8+ T cell exhaustion in these populations by evaluating the expression of multiple well-established phenotypic markers of exhaustion, as well as their transcriptomic signature.

Transcriptomic analysis of sorted tetramer+ cells. The Sekaly Laboratory will perform transcriptomic analysis of FACS sorted tetramer-detectable populations using RNASeq methods optimized and validated for small cell populations[10] and analyzed using validated bioinformatic pipelines for gene expression analysis. Transcriptomic profiling of longitudinal samples will enable characterization of vaccine and cytokine adjuvants on host gene expression. In addition, consideration of the gene expression data within the context of the aforementioned immunologic measurements will allow us to identify specific host transcriptomic correlates of vaccine responsiveness.

Antibody assays. The Alter Laboratory will perform a suite of functional assays covering a range of effector mechanisms (ADCC, phagocytosis, complement-mediated destruction, neutrophil activation, and dendritic cell uptake) carried out by a diverse set of innate effector cells (monocytes, NK, dendritic cells, and neutrophils) coupled to Systems Biology computational analyses[11]. This approach will be utilized to assess antibody functionality induced following therapeutic vaccination. This "Systems Serology" platform co-interrogates the biophysical features (antibody isotype/subclass and glycosylation), with all functional features to define the specific biophysical characteristics of both bulk and HIV-specific antibodies, creating a function:biophysical features map that may point to the specific antibody subpopulations that may 1) serve as biomarkers of enhanced reservoir control or 2) highlight mechanisms by which antibodies can contribute to control of the viral reservoir.

8.13 Virologic Measures

Ultrasensitive qPCR diagnostics will be used to quantify HIV RNA to single-copy levels.

Cell-associated (CA) total RNA[12] and integrated DNA[13] will be quantified using qPCR assays where nucleic acid input is normalized to cell number.

Since the mQVOA only detects intact proviruses that are induced by a single round of stimulation *in vitro* and replicate in MOLT cells[14], the Siliciano Laboratory will use a novel and scalable multiplex digital droplet PCR assay to measure the *total* number of intact proviruses. This assay is based on studies in which a large number of patient-derived, full-length proviruses have been characterized at the level of individual provirus.

8.14 Leukapheresis

Leukapheresis will be performed at Week -4 to -2 prior to entry and within 14 days after the Week 14 visit. The UCSF-based group already has an IRB-approved study in place which allows for leukapheresis to be performed on HIV-infected subjects (PI: Steven Deeks, MD, "The Use of Leukapheresis to Support HIV Pathogenesis Studies", 10-03244). The UCSF Options/SCOPE teams have performed over 200 research leukaphereses on HIV-infected individuals without any adverse events, typically yielding 5-17x10^9 (average 8x10^9) total cells, more than sufficient for characterizing viral reservoirs in sorted Tn, Tscm, Tcm, Ttm, and Tem subpopulations[15]. Leukapheresis product collected at UCLA will be shipped to UCSF for processing.

8.15 Colorectal biopsy

The UCSF-based group already has an IRB-approved study in place (PI: Ma Somsouk, MD, "Impact of HIV on Gut-Associated Lymphoid Tissue," 10-01218) which will allow for specimen collection and archiving of GALT samples. Participants enrolled in this study at UCSF will have the option to participate (co-enroll) in the colorectal biopsy study at least 2 weeks prior to Day 0 and approximately 2 weeks after the last vaccination (week 14).

8.16 Sample processing and specimen management

Within the UCSF SCOPE infrastructure, initial sample processing is performed on peripheral blood and leukapheresis units. All samples at UCSF and UCLA are tracked through Laboratory Information Systems, such as LDMS, or in-house systems with sample storage inventories, multiple report formats, and Institutionally-managed data storage and back-up systems.

The SCOPE Program will use the AIDS Specimen Bank (ASB) for preserving and distributing study specimens. ASB provides an established infrastructure with expertise in specimen processing and storage. It has received >188,000 deposits and has distributed >192,000 specimen aliquots worldwide. Specimens are stored in ultra-low temperature freezers with back-up power systems, in which temperature is monitored by a programmable scanning alarm system wired into the university's telephone system.

9 EVALUATIONS BY VISIT

Participants will be consented by the Principal Investigator or the research team before any procedures take place. All efforts will be made to have all visits occur between 8am and 11am, in order to account for diurnal variation in CD4+ T cell count and other assays and to allow for same-day shipping and storage of samples at the UCSF AIDS Specimen Bank.

Once a participant is identified as potentially eligible by phone screening and is to be scheduled for a screening visit, a unique identifier (SCOPE ID) will be assigned. Once a SCOPE ID is assigned, it cannot be reassigned to another subject.

Subjects who satisfy all inclusion/exclusion criteria will be enrolled into the study, which is summarized in the Schedule of Events.

	S	**B1**	**B2 D0[a]**	**W1**	**W4[a]**	**W8[a]**	**W12[a]**	**W14**	**W24**	**W36**	**W48**	**W64**	**Premature D/C**
Window		-4 to -2 weeks		+/- 3 days					+/-7 days				
Vaccine/placebo			X		X	X	X						
Distribute PRD			X		X	X	X						
Review PRD				X		X	X	X					
Concomitant Medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History[c]	X	X	X										
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X		X	X	X	X	X	X	X	X	X		X
T cell count, plasma HIV RNA	X	X	X		X			X	X	X	X	X	X
Pregnancy testing	X		X		X	X	X						
Cryopreservation plasma		X	X		X	X		X	X	X	X	X	X
Cryopreservation PBMCs			X						X		X	X	X
PAXgene tube collection		X						X			X		

Leukapheresis		X						X[b]					
Colorectal biopsy (optional)		X						X					

B=Baseline, D/C = discontinuation

[a]Participants should be contacted the day following each vaccination day to assess symptoms and response to injections

[b]Leukapheresis should occur within 14 days after week 14

[c]Concomitant Medications, Medical History, and Clinical Assessments will be assessed utilizing SCOPE questionnaires and study-specific forms at each indicated visit.

- Screen: All screening, enrollment, and consent procedures will be completed, including screening laboratory and clinical evaluations. All participants are assigned a unique four digit number. For those already enrolled in SCOPE, we will continue to use their existing number. New participants will be assigned a unique number during screening. Once a SCOPE ID is assigned, it cannot be reassigned to another subject. Hematology and chemistry laboratories will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Screening evaluations should be completed within 60 days prior to study entry.
- Week -4 to -2 (The first baseline (B1) visit): A leukapheresis will be performed. An optional gut biopsy will be scheduled and performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Hematology laboratories will be performed. Plasma will be collected and cryopreserved. A PAXgene specimen will be collected.
- Week 0 (Entry, B2 D0): The second baseline visit will occur. Subjects will initiate randomized treatment. Study product (vaccine or placebo) will be administered by electroporation. Routine safety studies (hematology and chemistry laboratories) will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma and PBMCs will be collected and cryopreserved. The PRD will be distributed.
- Day 1: Subjects will be contacted by telephone to check on symptoms and overall response to the injections.
- Week 1: Routine safety studies will be performed. The Day 0 (first dose) PRD will be reviewed.
- Week 4: The second vaccination will occur. Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma will be collected and cryopreserved. The PRD will be distributed.
- Week 4 + 1 Day: Subjects will be contacted by telephone to check on symptoms and overall response to the injections.
- Week 8: The third vaccination will occur. Routine safety studies will be performed. Plasma will be collected and cryopreserved. The Week 4 (second dose) PRD will be reviewed and a new PRD will be distributed.
- Week 8 + 1 Day: Subjects will be contacted by telephone to check on symptoms and overall response to the injections.

- Week 12: The final vaccination will occur. Routine safety studies will be performed. The Week 8 (third dose) PRD will be reviewed and a new PRD will be distributed.
- Week 12 + 1 Day: Subjects will be contacted by telephone to check on symptoms and overall response to the injections.
- Week 14: Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. A leukapheresis will be performed. Optional gut biopsy will be scheduled. Plasma will be collected and cryopreserved. A PAXgene specimen will be collected. All primary immunologic outcomes will be studied using specimens collected on this date.
- Week 24: Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma and PBMCs will be collected and cryopreserved.
- Week 36: Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma will be collected and cryopreserved.
- Week 48: Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma and PBMCs will be collected and cryopreserved. A PAXgene specimen will be collected.
- Week 64: Hematology, plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma and PBMCs will be collected and cryopreserved. All primary virologic outcomes will be studied using specimens collected on this date.
- Premature discontinuation: Routine safety studies will be performed. Plasma HIV RNA levels and CD4+/CD8+ T cell counts will be measured. Plasma and PBMCs will be collected and cryopreserved.

10 EXPERIENCE REPORTING AND DOCUMENTATION

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

10.2 AE Severity

The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1 (July 2017) (http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables) should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not specifically identified in the DAIDS grading table, the guidelines shown in Table 1 below should be used to grade severity. All deaths related to an AE are to be classified as grade 5. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Mild symptoms causing no or minimal interference with usual social and functional activities with intervention not indicated. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Moderate symptoms causing greater than minimal interference with usual social and functional activities with intervention indicated.
Severe (3)	Severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated.
Potentially Life-threatening (4)	Potentially life-threatening symptoms causing inability to perform basic self-care functions with intervention indicated to prevent permanent impairment, persistent disability, or death.

10.3 AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Related	There is a reasonable possibility that the AE may be related to the study agent(s).
Not related	There is not a reasonable possibility that the AE is related to the study agent(s).

10.4 Serious Adverse Events (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Death during the period of surveillance defined by the protocol
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

10.5 Serious Adverse Event Reporting

Study sites will document all SAEs that occur (whether or not related to study drug or device). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

All SAEs that are related to study drug or device will be reported. In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC. SAEs will also be reported to the U.S. Food and Drug Administration (FDA) per the reporting requirements specified by 21 CFR 312.32, with copy to the DAIDS Medical Officer (MO) and Inovio. Details of all related SAEs will be sent to the SMC and DAIDS MO no later than 3 reporting days after the investigators become aware of the event. For the purposes of expedited reporting to the SMC and the DAIDS Medical Officer, the definition of a "reporting day" in Version 2.0 of the DAIDS EAE Manual will be used.

10.6 Unanticipated (Serious) Adverse Device Effect (UADE)

A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application

(including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. Per the definition above, a UADE is a type of SAE that requires expedited reporting on the part of the Sponsor.

The study team will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

10.7 Medically attended adverse events

We will be using an IL-12 DNA adjuvant. This adjuvant theoretically might be associated with the induction of autoimmune or auto-inflammatory diseases. We will collect, analyze and report all data related to any medically attended adverse events (MAAEs), including potentially immune-mediated medical conditions (Appendix 2), through week 64 (one year after the last vaccine). The potential relatedness of any MAAE to the investigational product will be assessed. Any potentially vaccine-related immune-mediated medical condition will be categorized as unexpected.

10.8 Protocol Defined Important Medical Findings Requiring Real Time Reporting

Local reactions. Based on extensive experience with the study products, the only expected adverse events will be local discomfort and pain, which is always transient. Study subjects will be directly observed by study personnel for 30 minutes after each injection for immediate reactions. The occurrence and severity of any AE during this period or the lack of same will be recorded on the appropriate CRF using the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, Section on Site Reactions to Injections and Infusions.

Local reactions of mild (Grade 1) or moderate (Grade 2) severity will usually resolve spontaneously. If needed, they may be managed with local application of cold packs, oral acetaminophen, oral nonsteroidal anti-inflammatory agents, or a combination of these measures as appropriate.

The protocol team will be notified of all Grade 3 or 4 local toxicities within 48 hours of occurrence for consideration of modification or discontinuation of immunizations. For example, if a subject develops an intolerable local swelling (Grade 3 on the pain/tenderness scale) during the 72 hours after immunization, the protocol team should be contacted.

For Grade 4 local reactions, definitive medical and/or surgical intervention should be undertaken as appropriate.

Blood drawing (venipuncture) risks. Drawing blood from a vein may cause some discomfort, bleeding, or bruising where the needle enters the skin, and rarely, fainting or infection may occur. Up to a total of 1500 mL (about 3 pints) of blood will be drawn over the entire study period. No more than 480 mL (2 cups) of blood will be drawn over any two-month period. This is within Red Cross Guidelines (less than 500 mL every two months). Risks of blood collection include anemia (low blood counts). Symptoms of anemia include tiredness, weakness and dizziness. Subjects will be checked for anemia at each visit. If the investigator feels that a subject is at significant risk for anemia, the amount of blood collected will be reduced. If hemoglobin falls below 9 g/dL or hematocrit falls below 27%, subjects will have 5 mL (1 teaspoon) of blood drawn to check hemoglobin and hematocrit. Other than the blood required to check hemoglobin

and hematocrit, subjects will not have more blood drawn until hemoglobin rises above 9 g/dL or hematocrit rises above 27%.

10.9 Procedures for Documenting Pregnancy During the Trial

Subjects who are pregnant or expect to become pregnant during the course of the trial will be excluded from participation in the trial. Should a subject become pregnant after enrolling in the trial, she will not be given any further treatments with study drug or device. A Pregnancy Form will be completed by the Investigator and submitted to the study team and DAIDS MO within 24 hours after learning of the pregnancy. The Investigator will also report this event to the IRB within 24 hours of becoming aware of the pregnancy. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. When permission is received, subjects will continue to be followed for safety assessments to trial discharge per protocol. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the trial will continue to be followed for safety assessments without receiving further study drug or device. Procedures that are contraindicated during pregnancy, including additional treatments, must not be performed. Investigators should use clinical judgment regarding subsequent trial-related blood collection based on the presence or absence of anemia in each subject.

All pregnancies that occur from the time of first screening procedure through the follow-up visits must be reported. The Investigator will monitor the subject and follow the outcome of the pregnancy. If the end of the pregnancy occurs after the trial has been completed, the outcome will be reported directly to the trial team and the DAIDS MO.

Male subjects will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant until the end of follow-up period. A Pregnancy Form will be completed by the Investigator and submitted to the study team within 24 hours after learning of the pregnancy. Attempts will be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject exposed to study drug or device. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male subject or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

10.10 Reporting of Device Related Complaints or Deficiencies

A product complaint/device deficiency is defined as any written, electronic, or oral communication that alleges deficiencies or inadequacies of the device or components related to the identity, quality, durability, reliability, safety, effectiveness, or performance of the device or components after it is released for distribution within the clinical investigation. All product complaints that meet this definition (with the exception of SAEs requiring 24 hr reporting) must be reported to Inovio with 10 days of discovery.

Device Deficiencies include malfunctions, use errors and inadequate labeling. A malfunction is defined as the failure of a device to meet its performance specifications or otherwise perform as

intended. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Any problems experienced during the treatment procedure including potential malfunctions of the device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure must be reported to the Sponsor or designee immediately for evaluation. The error reporting or complaint form must be completed and emailed to Inovio at clinicalcomplaint@inovio.com.

11 CLINICAL MANAGEMENT ISSUES

Subjects may be offered topical anesthetic (e.g. EMLA or equivalent), to prevent significant discomfort from the treatment procedure. If a topical anesthetic is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to treatment. Subjects may be offered a non-narcotic analgesic (e.g. ibuprofen, ketorolac) after injection/EP.

Vaccination may be deferred for clinical or safety concerns such as febrile intercurrent illness at the discretion of the study investigator. Management of an individual participant should be determined by the study investigator with consultation with the study team.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation

A subject may be discontinued from study treatment at any time if the subject or the study team feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study
- Positive pregnancy test (females)
- Request for withdrawal by the subject's regular doctor

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early should have an early discontinuation visit.

12.3 Replacement of Subjects

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator, fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the study team and a Protocol Violation Form detailing the violation will be generated. A copy of the form will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 Data Sets Analyzed

All eligible patients who are enrolled into the study and who initiate therapy will be included in the safety and efficacy analysis. Analyses will be conducted by both intention-to-treat (primary) and per protocol. Low rates of non-adherence to study treatment and loss to follow up are anticipated (no more than 1 per arm for each).

14.2 Safety Analysis

All subjects will be followed for possible AEs throughout their involvement in the study. Routine blood work will be performed on a regular basis. AEs will be graded according to the DAIDS Table for Grading the Severity of Adults and Pediatric Adverse Events, Corrected Version 2.1, July 2017 (http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables). The Principal Investigator will review these data daily, assess their degree of severity, and make a relationship assessment to study agent/intervention. A study data coordinator will produce administrative reports after completion of each cohort describing study progress including the following: (1) accrual, (2) demographics, (3) study subject status, and (4) number and type of serious AEs. The Safety Monitoring Committee (SMC) will review study progress, efficacy data, all interim and total AEs, and unanticipated problems involving risk to participants. Reviews will be communicated to the UCSF and UCLA Institutional Review Boards, study sponsor, and/or federal agencies, as appropriate. The study will be discontinued if the SMC determines that it is in the best interest of the subjects.

Safety will be assessed by tabulating specific SAE's, SAE's judged to be treatment-related, and the occurrence of any one or more SAE, and by comparing these rates between active and placebo participants; comparisons will be made using Fisher's exact tests.

14.3 Data Analysis Plan

We will follow standard good statistical practices, including examination of summary statistics, assessment of model assumptions, examination and presentation of graphical depictions of the data, assessing the impact of influential data points, and interpretation that reflects the quantitative information provided by estimated effects and their confidence intervals, rather than an exclusive focus on whether or not $p<0.05$.

Primary endpoints: Counts and proportions of adverse events will be presented in frequency tables and characterized for each arm with 95% Clopper-Pearson Confidence Intervals.

The magnitude of response at the follow-up will be presented based on appropriate measures of central tendency (mean or median) and variability (standard deviation or interquartile range) in the T cell responses in each treatment arm. Additionally, to assess presence of center – by – treatment interaction, the T cell responses will be described within each center by treatment arms. Comparisons will be performed based on appropriate test, independent samples t-test or Wilcoxon.

Breadth of response will be characterized by the proportion of participants with at least one additional epitope response at week 14 (2 weeks after last vaccination) compared to their baseline response. The observed proportion of participants with response in breadth so defined will be presented with 95% Clopper-Pearson Confidence Intervals for each treatment arm. The proportion will also be assessed within each center for each treatment arm to examine potential center by treatment interaction. Comparisons will be performed using Binomial exact test.

Given stratification, we will compare T cell responses between strata within each arm. Should there be statistically significant differences between strata, subsequent analyses will be performed with adjustment, e.g. interaction, by strata.

Similar analyses will be conducted comparing T cell responses in Cohort B with Cohort A, gag/pol/env+IL-12 treated arm, to assess the correlation between early ART initiation and response to vaccination. As feasible, we will also compare T cell responses within Cohort B by Fiebig stage.

Secondary and the Other Endpoints: Descriptive analyses and inferences outlined for the Primary endpoints will be applied to the Secondary and the Other endpoints. Some measures, such as integrated DNA and cell-associated RNA, will likely be better modeled by negative binomial regression, as they tend to have a skewed distribution. In addition, it may be desirable to account for the amount of input to the assays, which is readily done in negative binomial models by inclusion of an "exposure" variable. In these cases, and also when linear regression or t-tests of logarithmically transformed measurements are appropriate, we will report relative effects (percentage or fold). Because nonparametric methods such as the Wilcoxon signed-rank test produce only p-values with no quantitative effect estimates, we will use these only as confirmatory analyses or when no quantitative analysis appears viable.

Statistical analyses for all aims will follow standard good statistical practices, including assessment of model assumptions, checking for influential observations, and interpreting results in light of estimated effects and their confidence intervals, in addition to p-values.

Trajectories of continuous measures evaluated longitudinally will be examined using mixed effects models with random slopes and/or intercepts, as appropriate. Similarly, categorical measures such as the number of "new" positive responses, the number of responses that remain negative, will be investigated in generalized mixed effects models. The models will be parameterized to address key issues, such as the difference in the speed of change in immunogenicity between the treatment arms through the interaction. Specifically, for many reservoir measures, we anticipate using negative binomial regression, because it can properly account for skewed distributions, observed values of zero, and varying amounts of input to the assays, while estimating relative effects (fold or percentage), which will be the most meaningful scale for many of the measurements. Whenever possible, we will also calculate and analyze a single summary measure over the entire treatment period for each person, e.g., the area under the curve and over baseline for immunogenicity measures over time. We note that the above approach can perform paired comparisons in the cases where the main interest focuses on the final measurement versus pre-treatment, although in those cases we will also employ simpler methods such as paired Student's *t*-tests when feasible.

14.4 Sample Size and Randomization

The objective of this study is to compare the safety, immunogenicity and anti-reservoir activity of PENNVAX-GP® (gag/pol/env)+IL-12 vs gag/pol+IL-12 vs placebo. Given experience with these vectors in the past, we do not expect to observe any significant adverse events. Also, given the lack of a latency reversing agent and a treatment interruption, an impact on the reservoir may not be possible. Hence, the virologic studies will be exploratory. Most of the analytic work in our program will hence focus on the extensive immunology that will be done before and after vaccination.

Sample Size Considerations. The proposed sample size provides sufficient (80%) power to detect a difference between study arms in safety and tolerability measures with an effect of size 1.1 [1.2] at the two-sided 0.05 [0.05/3, Bonferroni adjustment for multiple testing] significance level. The minimum detectable difference in comparisons of the baseline to the follow-up is 0.8 [0.9] at the two-sided 0.05 [0.05/3, Bonferroni adjustment for multiple testing] significance level. With a conservative estimate of one grade ≥3 adverse event, 95% CI for the proportion of one grade ≥3 adverse events in non-placebo arms (n=45) is (0.00056, 0.118), in all arms (n=60) is (0.000,0.089), and the 95% CI in a single study arm is (0.0017, 0.32).

With a more conservative estimate of two grade ≥3 adverse events, 95% CI for the proportion of grade ≥3 adverse events in non-placebo arms (n=45) is (0.005, 0.15), in all arms (n=60) is (0.004, 0.115), and the 95% CI in a single study arm is (0.017, 0.40). The same estimates apply to the tolerability proportions. Additionally, the proposed sample provides 95% assurance for the detection of at least one safety event if a true rate of occurrence is approximately 3%.

A 95% Clopper-Pearson Confidence Interval for measures of safety and tolerability defined in terms of proportion of events is estimated to have length of 0.218 for zero events and 0.318 for 1 event and sample size of 15 (one arm).

For the analysis comparing breadth of T cell responses between any two arms, a sample of 15 participants per arm achieves sufficient (80%) power to detect a difference in the proportion of participants with at least 1 epitope response that is ≥ 0.35 [0.45] at the two-sided 0.05 [0.05/3, Bonferroni adjustment for multiple testing] significance level using two-sample Binomial test of proportions. These calculations are performed with a conservative in terms of statistical power assumption that one response will be observed in the placebo arm by chance alone.

A sample of 15 participants per arm achieves sufficient (80%) power to detect a difference in the magnitude of response between the treatment arms that is at least 1.1[1.2]*SD at the two-sided 0.05 [0.05/3, Bonferroni adjustment for multiple testing] significance level. For paired before-after comparison within an active arm the difference is 0.8[0.9]*SD at the two-sided 0.05[0.05/2] significance level.

Use of repeated-measures analysis will improve power and precision. A recent study[6] observed effects that are larger than the minimum differences for ≥80% power, thus demonstrating that our proposed study has high power for likely differences.

Randomization and Stratification. For Cohort A, the three arm study of PENNVAX-GP® (gag/pol/env)+IL-12 vs gag/pol+IL-12 vs placebo in participants who initiated HIV treatment during chronic infection, participants will be randomized 1:1:1 within site and stratified on nadir CD4 <200 and ≥200 cells/mm^3, using block sizes of 3.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Detailed interviews (as part of the existing SCOPE protocol) will be conducted at each visit, including questions regarding current medications, medication adherence, intercurrent illnesses, and hospitalizations. We will use the UCSF CHR-approved SCOPE questionnaires for this study (PI, Steve Deeks, MD, "Study on Consequences of Protease Inhibitor Era: A Prospective Study" 10-01330).

Subjects will not be identified by name in the study database or on any study documents, but will be identified by a four digit number.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

All data will be managed by the UCSF Data Coordinating Center in the Department of Epidemiology and Biostatistics. Issues related to data management, specimen storage, and data analysis will be directed by Dr. Jeffrey Martin, who co-directs the SCOPE cohort with Dr. Deeks. Study participants will complete an interviewer-administered questionnaire modified to support the unique aspects of our proposed study (including collection of detailed information regarding sexual activities in both the study participant, and his or her partners). The standard system is compliant with all Federal Government confidentiality guidelines.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Clinical site monitoring visits will be conducted by representatives of DAIDS according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (UCSF), DAIDS, and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

The study data manager and statistician will prepare a quarterly report of accrual, early study treatment and study discontinuations (and related reasons), baseline characteristics, Grade ≥2 signs and symptoms, Grade ≥2 laboratory abnormalities and reported SAEs. Tables in the report will be based on the entire cohort of subjects and will not be stratified by treatment arm. This report will be reviewed by the study team, including the DAIDS MO or designee, on a quarterly basis.

A Study Monitoring Committee (SMC) will monitor study progress and participant safety, with one member of the SMC designated to serve as an Independent Safety Monitor (ISM). Approximately 6 months after enrollment of the first participant and then biannually, the SMC will meet and review accrual (including screening and enrollment), AE summaries, including all reported Grade ≥3 AEs, retention of participants including off-study rates, and longitudinal summaries of HIV-1 RNA by commercial assay and CD4+ T-cell count. In addition, the SMC will review sample collection and availability summaries for viable PBMCs and plasma.

In addition to the regularly scheduled reviews, the SMC will perform expedited reviews of the safety data, unblinded to treatment assignment, whenever any of the following happens:

- Three or more participants have experienced a grade 3 AE that is deemed possibly, probably, or definitely related to study treatment
- Two or more participants have experienced a grade 4 AE that is deemed possibly, probably, or definitely related to study treatment
- Any death occurs on study that is deemed possibly, probably, or definitely related to study treatment

Whenever any of the events above occurs, enrollment into the study will be paused until the SMC review has taken place and a determination has been made that enrollment can resume. The SMC will recommend, based on the results of the review, whether the study can proceed as planned, proceed with modifications, or should be discontinued.

The SMC may also be convened if a reason is identified by the study team, DAIDS MO, or study statistician.

The SMC will review progress towards pre-specified benchmarks of enrollment and retention of subjects, completion of study procedures, and collection of viable samples. If progress towards any benchmark is not adequate, as determined by the SMC, the SMC will recommend protocol modification if necessary.

Any recommendation for modification of the protocol will be made to DAIDS as well as the protocol team, and any amendment to the protocol will require DAIDS Clinical Science Review Committee (CSRC) approval. All updated versions of the protocol, IB, and related documents will be provided to the DAIDS MO and DAIDS Program Officer (PO).

The DAIDS MO and DAIDS PO will receive all safety-related documents sent to the FDA at the time they are reported to the FDA or earlier. The DAIDS MO and DAIDS PO will also receive copies of any correspondence received from the FDA.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a four-digit subject number will identify all study subjects on CRFs.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA and other local, US or international regulatory entities. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by PI. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. Any amendment to the protocol requires CSRC approval. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to any sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect

adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25, CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form will be given to the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
    1. Personally conduct or supervise the study (or investigation).
    2. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
    3. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
    4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.

5. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
6. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
7. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
8. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
9. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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SAMPLE INFORMED CONSENT FOR COHORT A

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Safety, immunogenicity and anti-reservoir activity of an electroporation-administered HIV DNA vaccine encoding Gag, Pol and Env proteins with IL-12 plasmid in HIV-infected adults on antiretroviral therapy

Short Title: Safety and Efficacy of an HIV DNA Therapeutic Vaccine

Introduction

You are being asked to take part in this research study because you have HIV infection, are taking anti-HIV medications (known as antiretroviral therapy, or "ART"), and the HIV virus (the virus that causes AIDS) that you are infected with has been kept at a very low level for at least 2 years.

This study involves research. Research is not the same as medical care. Research answers scientific questions. These answers can help find new medicines, treatments, vaccines, and even knowledge on how the human body works. Medical research studies include only people who choose to take part. This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why is this study being done?

Antiretroviral therapy (ART) prevents HIV from replicating and spreading but it does not cure HIV. Therapy for HIV must be taken daily for life. This study is attempting to find a way for the immune system to control HIV even after therapy is stopped. This will be achieved by using a vaccine that stimulates the immune system to more strongly recognize the virus. The study is inspired by recent success using a vaccine for the treatment of human papillomavirus (HPV), another chronic virus infection. Although the study team believes a vaccine such as the one being studied here will be helpful for finding a way to allow people with HIV to remain healthy off of therapy, it is not expected that the vaccine will work alone. The study vaccine will hence not cure HIV on its own.

Three vaccine products will be studied. The goals of the study are to see how safe the vaccine products are, how bothersome the side effects are from receiving the vaccine, and to understand the kinds of immune system responses the vaccine creates. These same vaccines have been given to HIV-uninfected persons in a separate research study. Other similar vaccines have been given to HIV-uninfected individuals and one study of HIV-infected individuals. In these studies, the vaccines were found to be safe and the main side effect was of pain at the injection site, which

passed quickly. Two of the vaccine products are made up of part of the natural human immunodeficiency virus (HIV). These products cannot replicate or grow in your body. One product contains information for the viral Gag and Pol proteins. The other product contains information for the viral Env protein. The third part of the vaccine is IL-12 and is designed to improve your body's response to the vaccine. IL-12 is naturally made by your body and helps to stimulate the immune system.

The vaccines are made of DNA. DNA contains the information needed to make new proteins. The DNA is taken up by certain cells in your body. These cells will make HIV proteins and IL-12 that stimulate your immune system.

We are interested in determining the best viral proteins to produce in an HIV vaccine. We will compare what happens in people who get either no active vaccine (placebo), a vaccine with just the Gag, Pol and IL-12 DNA and a vaccine with Gag, Pol, Env and IL-12 DNA.

The vaccines are injected into your body using an investigational device (called CELLECTRA®) through a process called "electroporation," or "EP." "Investigational" means the vaccine and study device combination being tested have not been approved by the Food and Drug Administration (FDA). The vaccines are given by a shot in the arm or leg, into the muscle. The CELLECTRA® device will deliver a short electric charge to increase the amount of the vaccine taken up by cells in your muscle. The vaccine is given with this device because EP appears to increase the body's response to vaccination compared to injection into the muscle alone.

Who is paying for this study?

This study is paid for by the NIH with support from Inovio (the manufacturer of vaccine).

How many people will take part in this study?

A total of 45 HIV-infected adults will be enrolled in this study.

How long will I be in this study?

The study will last for 64 weeks.

What will happen during the screening process?

If you decide to take part in this research study, you will be asked to sign this consent form and have a screening visit to determine if you can join the study. You will need to have the following "screening" exams, tests, or procedures to find out if you can be in the main part of the study:

Physical exam: You will have a complete physical examination, similar to that done for regular medical care. Your vital signs, height and weight will be measured.

Medical chart review: Your medical chart will be reviewed by the study staff.

Blood drawing (venipuncture): You will have blood drawn by inserting a needle into a vein in your arm or hand. Blood will be collected for laboratory tests to evaluate your general health and your HIV status (viral load, T cell counts).

Pregnancy testing: If you are a woman able to become pregnant, a pregnancy test (urine or blood) will be performed to confirm you are not pregnant. You will not be able to enroll in this study if you are pregnant.

You will be asked to remain on your current antiretroviral drugs throughout the study. The study will not provide any antiretroviral drugs.

What will happen during the main part of the study

If the screening tests determine that you can participate in the study and you choose to take part, then you will be enrolled in the study.

Once you are enrolled in the study you will be randomized to one of three groups to receive either:

1) Placebo (no vaccine AND no IL-12)
2) Gag, Pol, and IL-12 vaccine, or
3) Gag, Pol, Env, and IL-12 vaccine

Randomization is like flipping a coin. Neither you nor the study team will know which of the three treatments you will receive. You will have an equal chance of being in any one of these groups.

You will be asked to come to the clinic several times over the course of the study. You will have a physical exam and blood for routine studies and for research studies will be taken at each visit. You will be asked questions about your symptoms, medical history, diagnoses, and medications.

The first formal visit will be a baseline visit. This visit will occur approximately two weeks before the vaccines begin. At this time you will have blood collected during a procedure called leukapheresis. This procedure will remove blood from your arm, take out your white blood cells, and give back the rest of the blood. Two needles attached to tubes will be inserted into veins in each arm. Low calcium levels can occur from an additive (citric acid, similar to what is contained in fruit) that is used during the leukapheresis procedure to prevent your blood from clotting when it is in the machine. You may be given a small amount of intravenous or oral calcium to decrease symptoms related to having low calcium levels. You may also be given calcium to take if you develop numbness or tingling symptoms that suggest low calcium levels. At the completion of the leukapheresis procedure, the needles and tubes will be removed and you will be checked for bleeding before you are released. This is generally a three to four hour procedure.

You will start the vaccine series at the Week 0 visit. Following the first vaccine at the Week 0 visit, you will be asked to return to the clinic at Week 1 for blood studies. You will then have vaccines at Weeks 4, 8 and 12. You will be observed in the clinic for 30 minutes following each vaccine. A study team member will call you approximately 24 hours after each vaccine to check if there are any problems. You will be asked to keep a diary of any symptoms you experience on the day of the study dosing and for 6 days after the study dosing.

You will be asked to return to the clinic two weeks after the last vaccine for more studies. This Week 14 visit will be when most of the important studies of your immune system will be performed. Another leukapheresis will occur at this time.

You will then be asked to return at Weeks 24, 36, 48 and 64 for more blood studies and to see if you have had any symptoms or medical conditions that may have been related to the vaccine.

Unscheduled visits:
During the study, you may have to return to the research unit for unscheduled visits for additional testing if you have any abnormal lab values or to follow-up on a specific side effect or symptom.

Referrals to other studies:
You may be asked to undergo additional studies to determine how the vaccines affect your immune system in the lining of your gut. These studies involve taking pieces of tissue from your gut. These are optional. A separate form will need to be signed.

Total collection of blood:
About 3 pints of blood will be drawn over the entire study.

Storage of blood for future research studies:
As part of this study, a portion of the blood (plasma, peripheral blood mononuclear cells, serum) obtained at some of the study visits will be stored at the University of California, San Francisco (UCSF) for future research studies. We will also collect and save information from your medical record, including results of physical examinations, diagnostic tests, medical questionnaires and histories, diagnoses, and treatments. We do not know if your specimens or medical record will be used, but they might be used in research to learn more about HIV infection. Only the study team will have direct access to the specimens.

All specimens are coded with an ID number. Only the date the specimen was collected will be stored with the specimen; no personal identifiers such as your name will be kept with stored specimens. Only the study team will know which samples belong to you.

We may give the specimen and certain medical information about you (for example, diagnosis, age) to other scientists or companies, but we will not give them your name, address, phone number, or any other information that would identify you. Your personal health information cannot be used for additional research without additional approval from either you or a review committee.

The following tests of your immune system and virus may be performed:
- Tests to determine how much virus is in your T cells
- Tests to determine the level of immune markers in your blood
- Other tests related to this study, which are unknown at this time, may be performed.

Your specimens will be kept indefinitely at UCSF. If you agree, any information obtained from laboratory studies that may be important for your clinical care will be shared with you and/or your primary care provider. This information, however, is exploratory and the clinical relevance and accuracy of the data are unknown. You should indicate at the end of this consent form if you want this information shared.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if we use the specimen for genetic research, we will not put the results in your medical record. The research will not change the care you receive. Your specimens and any information about you will be kept until it is used up or destroyed. The specimens may be used to develop new discoveries, drugs, tests, treatments, or products. In some instances these may have potential commercial value, but you will not receive any payment or financial benefit from any products, tests, or discoveries.

If you decide later that you do not want your specimens and information to be used for future research, you can tell the study principal investigator and any remaining identifiable specimens and information will be destroyed.

Medications not allowed during the study

You will be asked not to take any strong drugs that directly affect your immune system unless they are medically necessary. These might include prednisone and other power steroid drugs. You will also be encouraged not to change your antiretroviral drug regimen unless there are side effects or they stop working.

Can I stop being in the study?

You can decide to stop at any time. It is important to tell the study doctor or research staff if you are thinking about stopping or have decided to stop.

The study investigators may take you off the study early without your permission if:

- The study is stopped or cancelled.
- You are not able to attend the study visits as required by the study.
- The study doctor or you regular doctor thinks that the study is no longer in your best interest.
- You become pregnant.

The study investigators will supervise any discontinuation of study medications with you as your health is the first priority. You will be asked to have a final visit for a physical exam and laboratory tests and your treatment options will be discussed with you.

The study may be stopped at any time by the Food and Drug Administration, the (insert name of site) Institutional Review Board (IRB), and/or other appropriate regulatory agencies.

What side effects or risks can I expect from being in the study?

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You should talk to the study doctor or research staff about any side effects that you experience while taking part in the study.

Risks and side effects related to vaccine: The vaccines used in this study have been studied in the past. No major side effects have been reported and none are expected. Because the vaccine and device combination is investigational, all of the side effects may not be known. Below is a list of possible side effects of the vaccines, based on experience with similar investigational products delivered using the CELLECTRA® device.

Very Common Side Effects (>10%) are:

- Mild to moderate injection site pain or tenderness
- Injection site erythema or redness
- Injection site swelling
- Injection site pruritis (itching)
- Nausea
- Fatigue
- Myalgia
- Headache

Common Side Effects (1-10%) are:

- Malaise
- Injection site bruising
- Pyrexia (fever)
- Arthralgia

There may also be risks or side effects that are unknown and/or unforeseeable.

Risks of the CELLECTRA® device: The EP process is almost always associated with local areas of discomfort and swelling. These effects will go away in a few minutes to hours. During the procedure, you may feel pain where the needles are inserted. Other clinical trial participants have rated the discomfort that they felt during the procedure on a scale from 0 ("no pain") to 10 ("worst pain") and the average pain/score was around six (6) immediately after the procedure and less than one (1) at 10 minutes after the procedure.

Risks related to the leukaphereses:

- Pain or discomfort, bruising, swelling and possible infection may be associated with blood collection and insertion of the needles for leukapheresis. You may feel dizzy or faint. The pheresis staff will quickly treat any of these reactions and will direct their

efforts to preventing a reaction from occurring. Should any of these or any other reaction occur during the pheresis procedure, the procedure will be stopped until the problem has been rectified. At any time, if you feel uncomfortable or if you do not wish to proceed, the procedure will be stopped at your request.

- Risks associated directly with the leukapheresis are usually minimal but could include: tingling around the mouth and face, vibrating feeling, possible muscle cramps and feeling cold from the additives used to prevent your blood from clotting when it is in the machine.

- Less common symptoms include lightheadedness, dizziness, fainting, nausea and vomiting, hematoma or bruise caused by bleeding under the skin.

- Serious complications, though extremely rare, could occur and could include major blood loss or introduction of air bubbles into the bloodstream which can block blood circulation to the lungs and other vital organs, but the modern machines make this very unlikely.

- In very rare situations, the machine may malfunction and lead to clotting of your blood in the machine, or may damage some of your red blood cells that are in the machine. The machine is equipped with automatic safety devices that will stop the pheresis if these complications occur in order to prevent any possible harm to you. If such a shutdown does occur, it may be impossible to return to you all of the blood and plasma that are in the machine. The volume of blood which you may lose will be about one half unit of blood (8 ounces or one cup).

Reproductive risks: There are no adequate and well-controlled trials of these vaccines in pregnant women. It is not known whether the investigational products and/or device may affect an unborn child or nursing infant. For this reason, if you are breast-feeding, pregnant or plan to become pregnant, you cannot participate in this clinical trial. You will be asked to take a pregnancy test at the beginning of the clinical trial and before each dose of investigational products in order to determine if you are pregnant.

If you are able to become pregnant, two of the following forms of birth control are required, one of which must be condoms or a diaphragm or cervical cap:

- Condoms (male of female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD) with published data showing that expected failure rate is < 1% per year
- Tubal ligation
- Hormone-based contraceptive such as oral birth control pills

Even if you use acceptable forms of birth control during the clinical trial, there is a chance you could become pregnant. If you do become pregnant during the clinical trial:

- Call/notify the study doctor immediately
- Consult an obstetrician or maternal-fetal specialist
- You will not be given any additional investigational products

- You will be followed to determine the pregnancy outcome

If you are a male who is sexually active with a woman capable of becoming pregnant, you must agree to use a medically accepted form of birth control during the course of this research study. You should inform your partner of the potential harm to an unborn child. She needs to know that if she does become pregnant during the study:

- You will need to call/notify the study doctor immediately
- She will need to consult an obstetrician or maternal-fetal specialist
- We will ask for her permission to collect information about the pregnancy and the health of the baby. This includes information related to the pregnancy/delivery and obstetrical history. The data concerning the pregnancy and birth outcome will be held in a drug safety database.

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Risk of genetic testing: Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record.

Effect on participating in other studies: Every research study has different requirements for participation, which are known as eligibility criteria. If you participate in this study, the procedures required for this study may make you not eligible to participate in other studies for a period of time. How long that period of time is is determined by the other study.

Unknown risks: The vaccines may have side effects that no one knows about yet. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. For more information about risks and side effects, ask the study investigators or a member of the study team.

Are there benefits to taking part in the study?

If you take part in this study, you should not expect any direct benefit to you. Information learned from this study may help others who have HIV.

What other choices do I have if I do not take part in this study?

You may choose not to participate in this study. Antiretroviral therapy to treat HIV is available by prescription and is highly effective even without a vaccine. You should talk to your doctor about your choices before deciding to take part in this study.

Will my medical information be kept private?

We will do everything we can to protect your privacy. Participation in research involves some loss of privacy. We will do our best to make sure that personal information about you is kept private, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. A study record will be created because of your participation in this study. Your signed consent form and some of your research test results will be included in this record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Institutional Review Board (IRB) (a group that protects the rights and well-being of research participants)
- Office for Human Research Protections (OHRP) or other local, US, or international regulatory entities as part of their duties
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- Inovio Pharmaceuticals
- Study staff
- Study monitors

What are the costs of taking part in this study?

You will not be charged for the study medications, the study visits, examinations, or tests required by the study. You or your insurance company will need to cover the costs of your standard antiretroviral drugs (HIV medications). You or your insurance company will be responsible for the costs of your regular medical care as well as for the costs of the anti-HIV medicines that you will take after you complete the study.

Will I be paid for taking part in this study?

You will not be paid for the screening visit. If you are eligible for this study and choose to participate, in return for your time, effort, and travel expenses, you will be paid $XX at the

completion of each study visit (excluding the screening visit). For each leukapheresis procedure you undergo, you will be paid $XX.

Payments for participating in research studies are considered reportable income for tax purposes. The University of California will not report this income to the Internal Revenue Service (IRS) unless your total University income equals or exceeds $600 in a single calendar year. The University accounting procedures assure that your participation in this study remains confidential.

What happens if I am injured because I took part in this study?

It is important that you promptly tell the study investigators or staff if you feel that you have been injured because of taking part in this study. You can tell the investigator in person or call him/her at the number(s) listed below.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. There is no program for compensation through the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

For questions about this study, contact:

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please contact:

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

CONSENT

You have been given copies of this signed and dated consent form and the Experimental Subject's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____	_____
Date	Participant's Signature for Consent	Printed name of Participant

____	_____	_____
Date	Signature of Person Obtaining Consent	Printed name of Person Obtaining Consent

Optional consent to share any results from laboratory studies:

I ☐ agree ☐ do not agree to have ☐ my primary care provider and/or ☐ myself informed of any results from the laboratory studies that might be important to my care.

Subject's initials _____

OPTIONAL STUDIES

Optional Co-enrollment into gut biopsy study: At study entry, you will be asked if you want to enroll in a gut biopsy study. This study will allow us to measure changes in immune cells in the gut. Visits will be coordinated with visits required by this study. This is a separate study and requires a separate consent form. Participation in the gut biopsy study is not a requirement of this study. If you agree to participate in the gut biopsy study, you will be asked to sign a separate consent form.

SAMPLE INFORMED CONSENT FOR COHORT B

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: Safety, immunogenicity and anti-reservoir activity of an electroporation-administered HIV DNA vaccine encoding Gag, Pol and Env proteins with IL-12 plasmid in HIV-infected adults on antiretroviral therapy

Short Title: Safety and Efficacy of an HIV DNA Therapeutic Vaccine

Introduction

You are being asked to take part in this research study because you have HIV infection, you started anti-HIV medications (known as antiretroviral therapy, or "ART") very soon after you were first infected with HIV, you are currently taking anti-HIV medications, and the HIV virus (the virus that causes AIDS) that you are infected with has been kept at a very low level for at least 2 years.

This study involves research. Research is not the same as medical care. Research answers scientific questions. These answers can help find new medicines, treatments, vaccines, and even knowledge on how the human body works. Medical research studies include only people who choose to take part. This is a consent form. It gives you information about this study. The study staff will talk with you about this information. You are free to ask questions about this study at any time. Take your time to make your decision about participating. You may discuss your decision with your family and friends and with your health care team. If you have any questions, you may ask your study doctor. If you agree to take part in this study, you will be asked to sign this consent form. You will get a copy to keep.

Why is this study being done?

Antiretroviral therapy (ART) prevents HIV from replicating and spreading but it does not cure HIV. Therapy for HIV must be taken daily for life. This study is attempting to find a way for the immune system to control HIV even after therapy is stopped. This will be achieved by using a vaccine that stimulates the immune system to more strongly recognize the virus. The study is inspired by recent success using a vaccine for the treatment of human papillomavirus (HPV), another chronic virus infection. Although the study team believes a vaccine such as the one being studied here will be helpful for finding a way to allow people with HIV to remain healthy off of therapy, it is not expected that the vaccine will work alone. The study vaccine will hence not cure HIV on its own.

Three vaccine products will be studied. The goals of the study are to see how safe the vaccine products are, how bothersome the side effects are from receiving the vaccine, and to understand the kinds of immune system responses the vaccine creates. These same vaccines have been given to HIV-uninfected persons in a separate research study. Other similar vaccines have been given to HIV-uninfected individuals and one study of HIV-infected individuals. In these studies, the vaccines were found to be safe and the main side effect was of pain at the injection site, which

passed quickly. Two of the vaccine products are made up of part of the natural human immunodeficiency virus (HIV). These products cannot replicate or grow in your body. One product contains information for the viral Gag and Pol proteins. The other product contains information for the viral Env protein. The third part of the vaccine is IL-12 and is designed to improve your body's response to the vaccine. IL-12 is naturally made by your body and helps to stimulate the immune system.

The vaccines are made of DNA. DNA contains the information needed to make new proteins. The DNA is taken up by certain cells in your body. These cells will make HIV proteins and IL-12 that stimulate your immune system. We are interested in determining the best viral proteins to produce in an HIV vaccine.

The vaccines (investigational products) are injected into your body using an investigational device (called CELLECTRA®) through a process called "electroporation," or "EP." "Investigational" means the vaccine and study device combination being tested have not been approved by the Food and Drug Administration (FDA). The vaccines are given by a shot in the arm or leg, into the muscle. The CELLECTRA® device will deliver a short electric charge to increase the amount of the vaccine taken up by cells in your muscle. The vaccine is given with this device because EP appears to increase the body's response to vaccination compared to injection into the muscle alone.

Who is paying for this study?

This study is paid for by the NIH with support from Inovio (the manufacturer of vaccine).

How many people will take part in this study?

A total of 15 HIV-infected adults will be enrolled in this Cohort of the study.

How long will I be in this study?

The study will last for 64 weeks.

What will happen during the screening process?

If you decide to take part in this research study, you will be asked to sign this consent form and have a screening visit to determine if you can join the study. You will need to have the following "screening" exams, tests, or procedures to find out if you can be in the main part of the study:

Physical exam: You will have a complete physical examination, similar to that done for regular medical care. Your vital signs, height and weight will be measured.

Medical chart review: Your medical chart will be reviewed by the study staff.

Blood drawing (venipuncture): You will have blood drawn by inserting a needle into a vein in your arm or hand. Blood will be collected for laboratory tests to evaluate your general health and your HIV status (viral load, T cell counts).

Pregnancy testing: If you are a woman able to become pregnant, a pregnancy test (urine or blood) will be performed to confirm you are not pregnant. You will not be able to enroll in this study if you are pregnant.

You will be asked to remain on your current antiretroviral drugs throughout the study. The study will not provide any antiretroviral drugs.

What will happen during the main part of the study

If the screening tests determine that you can participate in the study and you choose to take part, then you will be enrolled in the study.

You will receive the vaccine containing Gag, Pol, Env and IL-12 DNA. The vaccine is given as a shot in the muscle of the upper arm or leg.

You will be asked to come to the clinic several times over the course of the study. You will have a physical exam and blood for routine studies and for research studies will be taken at each visit. You will be asked questions about your symptoms, medical history, diagnoses, and medications.

The first formal visit will be a baseline visit. This visit will occur approximately two weeks before the vaccines begin. At this time you will have blood collected during a procedure called leukapheresis. This procedure will remove blood from your arm, take out your white blood cells, and give back the rest of the blood. Two needles attached to tubes will be inserted into veins in each arm. Low calcium levels can occur from an additive (citric acid, similar to what is contained in fruit) that is used during the leukapheresis procedure to prevent your blood from clotting when it is in the machine. You may be given a small amount of intravenous or oral calcium to decrease symptoms related to having low calcium levels. You may also be given calcium to take if you develop numbness or tingling symptoms that suggest low calcium levels. At the completion of the leukapheresis procedure, the needles and tubes will be removed and you will be checked for bleeding before you are released. This is generally a three to four hour procedure.

You will start the vaccine series at the Week 0 visit. Following the first vaccine at the Week 0 visit, you will be asked to return to the clinic at Week 1 for blood studies. You will then have vaccines at Weeks 4, 8 and 12. You will be observed in the clinic for 30 minutes following each vaccine. A study team member will call you approximately 24 hours after each vaccine to check if there are any problems. You will be asked to keep a diary of any symptoms you experience on the day of the study dosing and for 6 days after the study dosing.

You will be asked to return to the clinic two weeks after the last vaccine for more studies. This Week 14 visit will be when most of the important studies of your immune system will be performed. Another leukapheresis will occur at this time.

You will then be asked to return at Weeks 24, 36, 48 and 64 for more blood studies and to see if you have had any symptoms or medical conditions that may have been related to the vaccine.

Unscheduled visits:

During the study, you may have to return to the research unit for unscheduled visits for additional testing if you have any abnormal lab values or to follow-up on a specific side effect or symptom.

Referrals to other studies:

You may be asked to undergo additional studies to determine how the vaccines affect your immune system in the lining of your gut. These studies involve taking pieces of tissue from your gut. These are optional. A separate form will need to be signed.

Total collection of blood:

About 3 pints of blood will be drawn over the entire study.

Storage of blood for future research studies:

As part of this study, a portion of the blood (plasma, peripheral blood mononuclear cells, serum) obtained at some of the study visits will be stored at the University of California, San Francisco for future research studies. We will also collect and save information from your medical record, including results of physical examinations, diagnostic tests, medical questionnaires and histories, diagnoses, and treatments. We do not know if your specimens or medical record will be used, but they might be used in research to learn more about HIV infection. Only the study team will have direct access to the specimens.

All specimens are coded with an ID number. Only the date the specimen was collected will be stored with the specimen; no personal identifiers such as your name will be kept with stored specimens. Only the study team will know which samples belong to you.

We may give the specimen and certain medical information about you (for example, diagnosis, age) to other scientists or companies, but we will not give them your name, address, phone number, or any other information that would identify you. Your personal health information cannot be used for additional research without additional approval from either you or a review committee.

The following tests of your immune system and virus may be performed:

- Tests to determine how much virus is in your T cells
- Tests to determine the level of immune markers in your blood
- Other tests related to this study, which are unknown at this time, may be performed.

Your specimens will be kept indefinitely at UCSF. If you agree, any information obtained from laboratory studies that may be important for your clinical care will be shared with you and/or your primary care provider. This information, however, is exploratory and the clinical relevance and accuracy of the data are unknown. You should indicate at the end of this consent form if you want this information shared.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if we use the specimen for genetic research, we will not put the results in your

medical record. The research will not change the care you receive. Your specimens and any information about you will be kept until it is used up or destroyed. The specimens may be used to develop new discoveries, drugs, tests, treatments, or products. In some instances these may have potential commercial value, but you will not receive any payment or financial benefit from any products, tests, or discoveries.

If you decide later that you do not want your specimens and information to be used for future research, you can tell the study principal investigator and any remaining identifiable specimens and information will be destroyed.

Medications not allowed during the study

You will be asked not to take any strong drugs that directly affect your immune system unless they are medically necessary. These might include prednisone and other power steroid drugs. You will also be encouraged not to change your antiretroviral drug regimen unless there are side effects or they stop working.

Can I stop being in the study?

You can decide to stop at any time. It is important to tell the study doctor or research staff if you are thinking about stopping or have decided to stop.

The study investigators may take you off the study early without your permission if:

- The study is stopped or cancelled.
- You are not able to attend the study visits as required by the study.
- The study doctor or you regular doctor thinks that the study is no longer in your best interest.
- You become pregnant.

The study investigators will supervise any discontinuation of study medications with you as your health is the first priority. You will be asked to have a final visit for a physical exam and laboratory tests and your treatment options will be discussed with you.

The study may be stopped at any time by the Food and Drug Administration, the (insert name of site) Institutional Review Board (IRB), and/or other appropriate regulatory agencies.

What side effects or risks can I expect from being in the study?

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- Risks associated directly with the leukapheresis are usually minimal but could include: tingling around the mouth and face, vibrating feeling, possible muscle cramps and feeling

cold from the additives used to prevent your blood from clotting when it is in the machine.

- Less common symptoms include lightheadedness, dizziness, fainting, nausea and vomiting, hematoma or bruise caused by bleeding under the skin.

- Serious complications, though extremely rare, could occur and could include major blood loss or introduction of air bubbles into the bloodstream which can block blood circulation to the lungs and other vital organs, but the modern machines make this very unlikely.

- In very rare situations, the machine may malfunction and lead to clotting of your blood in the machine, or may damage some of your red blood cells that are in the machine. The machine is equipped with automatic safety devices that will stop the pheresis if these complications occur in order to prevent any possible harm to you. If such a shutdown does occur, it may be impossible to return to you all of the blood and plasma that are in the machine. The volume of blood which you may lose will be about one half unit of blood (8 ounces or one cup).

Reproductive risks: There are no adequate and well-controlled trials of these vaccines in pregnant women. It is not known whether the investigational products and/or device may affect an unborn child or nursing infant. For this reason, if you are breast-feeding, pregnant or plan to become pregnant, you cannot participate in this clinical trial. You will be asked to take a pregnancy test at the beginning of the clinical trial and before each dose of investigational products in order to determine if you are pregnant.

If you are able to become pregnant, two of the following forms of birth control are required, one of which must be condoms or a diaphragm or cervical cap:

- Condoms (male of female) with or without a spermicidal agent
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD) with published data showing that expected failure rate is < 1% per year
- Tubal ligation
- Hormone-based contraceptive such as oral birth control pills

Even if you use acceptable forms of birth control during the clinical trial, there is a chance you could become pregnant. If you do become pregnant during the clinical trial:

- Call/notify the study doctor immediately
- Consult an obstetrician or maternal-fetal specialist
- You will not be given any additional investigational products
- You will be followed to determine the pregnancy outcome.

If you are a male who is sexually active with a woman capable of becoming pregnant, you must agree to use a medically accepted form of birth control during the course of this research study.

You should inform your partner of the potential harm to an unborn child. She needs to know that if she does become pregnant during the study:

- You will need to call/notify the study doctor immediately
- She will need to consult an obstetrician or maternal-fetal specialist
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Risk of genetic testing: Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies and/or employers regarding your health.

To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record.

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Unknown risks: The vaccines may have side effects that no one knows about yet. All drugs have a potential risk of an allergic reaction, which if not treated promptly, could become life-threatening. The researchers will let you know if they learn anything that might make you change your mind about participating in the study. For more information about risks and side effects, ask the study investigators or a member of the study team.

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You may choose not to participate in this study. Antiretroviral therapy to treat HIV is available by prescription and is highly effective even without a vaccine. You should talk to your doctor about your choices before deciding to take part in this study.

Will my medical information be kept private?

We will do everything we can to protect your privacy. Participation in research involves some loss of privacy. We will do our best to make sure that personal information about you is kept private, but we cannot guarantee total privacy. Some information from your medical records will be collected and used for this study. A study record will be created because of your participation in this study. Your signed consent form and some of your research test results will be included in this record. Therefore, people involved with your future care and insurance may become aware of your participation and of any information added to your medical record as a result of your participation. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Institutional Review Board (IRB) (a group that protects the rights and well-being of research participants)
- Office for Human Research Protections (OHRP) or other local, US, or international regulatory entities as part of their duties
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)
- Inovio Pharmaceuticals
- Study staff
- Study monitors

What are the costs of taking part in this study?

You will not be charged for the study medications, the study visits, examinations, or tests required by the study. You or your insurance company will need to cover the costs of your standard antiretroviral drugs (HIV medications). You or your insurance company will be responsible for the costs of your regular medical care as well as for the costs of the anti-HIV medicines that you will take after you complete the study.

Will I be paid for taking part in this study?

You will not be paid for the screening visit. If you are eligible for this study and choose to participate, in return for your time, effort, and travel expenses, you will be paid $XX at the completion of each study visit (excluding the screening visit). For each leukapheresis procedure you undergo, you will be paid $XX.

Payments for participating in research studies are considered reportable income for tax purposes. The University of California will not report this income to the Internal Revenue Service (IRS) unless your total University income equals or exceeds $600 in a single calendar year. The University accounting procedures assure that your participation in this study remains confidential.

What happens if I am injured because I took part in this study?

It is important that you promptly tell the study investigators or staff if you feel that you have been injured because of taking part in this study. You can tell the investigator in person or call him/her at the number(s) listed below.

Treatment and Compensation for Injury: If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. The costs of the treatment may be billed to you or your insurer just like any other medical costs, or covered by the University of California, depending on a number of factors. The University does not normally provide any other form of compensation for injury. There is no program for compensation through the National Institutes of Health. You will not be giving up any of your legal rights by signing this consent form.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

For questions about this study, contact:

If you wish to ask questions about the study or your rights as a research participant to someone other than the researchers or if you wish to voice any problems or concerns you may have about the study, please contact:

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

CONSENT

You have been given copies of this signed and dated consent form and the Experimental Subject's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

PARTICIPATION IN RESEARCH IS VOLUNTARY. You have the right to decline to participate or to withdraw at any point in this study without penalty or loss of benefits to which you are otherwise entitled.

If you have read this consent form (or had it explained to you), all your questions have been answered and you agree to take part in this study, please sign your name below.

_____	_____	_____
Date	Participant's Signature for Consent	Printed name of Participant

____	_____	_____
Date	Signature of Person Obtaining Consent	Printed name of Person Obtaining Consent

Optional consent to share any results from laboratory studies:

I ☐ agree ☐ do not agree to have ☐ my primary care provider and/or ☐ myself informed of any results from the laboratory studies that might be important to my care.

Subject's initials _____

OPTIONAL STUDIES

Optional Co-enrollment into gut biopsy study: At study entry, you will be asked if you want to enroll in a gut biopsy study. This study will allow us to measure changes in immune cells in the gut. Visits will be coordinated with visits required by this study. This is a separate study and requires a separate consent form. Participation in the gut biopsy study is not a requirement of this study. If you agree to participate in the gut biopsy study, you will be asked to sign a separate consent form.