A5379

B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe): Evaluation of HEPLISAV-B

A Multicenter Trial of the AIDS Clinical Trials Group (ACTG)

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SIGNATURE PAGE

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

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TABLE OF CONTENTS

CONTENTS (Cont'd)

Page

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STUDY MANAGEMENT

All general questions concerning this protocol should be sent to actg.teamA5379@fstrf.org via e-mail. The appropriate team member will respond with a "cc" to actg.teamA5379@fstrf.org. A response should generally be received within 24 hours (Monday through Friday).

Protocol E-mail Group
Sites should contact the User Support Group at the Data Management Center (DMC) as soon as possible to have the relevant personnel at the site added to the actg.protA5379 e-mail group. Include the protocol number in the e-mail subject line.

- Send an e-mail message to actg.user.support@fstrf.org.

Clinical Management:
For questions concerning entry criteria, toxicity management, concomitant medications, and co-enrollment, contact the Clinical Management Committee (CMC).

- Send an e-mail message to actg.cmca5379@fstrf.org. Include the protocol number, patient identification number (PID), and a brief relevant history.

Laboratory
For questions specifically related to immunologic laboratory tests, contact the Protocol Immunologist.

- Send an e-mail message to actg.teamA5379@fstrf.org (ATTENTION: Andrea Cox).

Data Management

- For nonclinical questions about transfers, inclusion/exclusion criteria, electronic case report forms (eCRFs), randomization/registration, and other data management issues, contact the data manager. Completion guidelines for eCRFs and participant-completed CRFs can be downloaded from the FSTRF website at www.frontierscience.org.
- For transfers, reference the Study Participant Transfer SOP 119, and contact Stephanie Caruso **and Lillian Collins** directly.
- For other questions, send an e-mail message to actg.teamA5379@fstrf.org (ATTENTION: Stephanie Caruso **and Lillian Collins**).
- Include the protocol number, PID, and a detailed question.

Randomization/Participant Registration
For randomization/participant registration questions or problems and study identification number SID lists:

- Send an e-mail message to rando.support@fstrf.org or call the DMC Randomization Desk at 716-834-0900, extension 7301.

DMC Portal and Medidata Rave Problems
Contact DMC User Support.

- Send an e-mail message to actg.user.support@fstrf.org or call 716-834-0900 x7302.

Protocol Document Questions
For questions concerning the protocol document, contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5379@fstrf.org (ATTENTION: Christina Vernon).

Copies of the Protocol
To request a hard copy of the protocol, send an e-mail message to ACTGNCC@dlhcorp.com. Electronic copies can be downloaded from the ACTG website at https://www.actgnetwork.org.

Product Package Inserts and/or Investigator Brochures
To request copies of product package inserts or investigator brochures, contact the DAIDS Regulatory Support Center (RSC) at RIC@tech-res.com or call 301-897-1708.

Protocol Registration
For protocol registration questions, send an e-mail message to Protocol@tech-res.com or call 301-897-1707.

Protocol Activation
For questions related to protocol activation at US sites, contact the Clinical Trials Specialist.
- Send an e-mail message to actg.teamA5379@fstrf.org (ATTENTION: Christina Vernon).

For questions related to protocol activation at non-US sites, contact the ACTG Site Coordination Group.
- Send an email message to actgsitecoordination@dlhcorp.com.

Study Products
For questions or problems regarding study products, dose, supplies, records, and returns, e-mail Oladapo Alli (oladapo.alli@nih.gov) and Shawn Chiambah (shawn.chiambah@nih.gov), Protocol Pharmacists.

Study Vaccine Orders
- For study products that will be centrally distributed by the Clinical Research Products Management Center (CRPMC), the site Pharmacist of Record must complete and return the Drug Supply Statement provided by the CRPMC after site protocol registration and place an order via the CRPMC's internet ordering system (CIOS). Any questions regarding study product orders and distribution should be directed to the CRPMC via e-mail (bio.crpmc.ph@thermofisher.com).
- For orders for ENGERIX-B at sites in Kenya, Peru, Thailand, Uganda, and Zimbabwe, country specific instructions can be found on the protocol-specific web page (PSWP*).*

IND (Investigational New Drug) Number or Questions
For any questions related to the IND submission, contact the DAIDS RSC at Regulatory@tech-res.com or call 301-897-1706.

Expedited Adverse Event (EAE) Reporting/Questions
Contact DAIDS through the RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com or call 1-800-537-9979 or 301-897-1709; or fax 1-800-275-7619 or 301-897-1710.

Telephone Calls

Sites are responsible for documenting telephone calls made to A5379 team members.

- Send an e-mail message to actg.teamA5379@fstrf.org.

Protocol-Specific Web Page

Additional information about management of the protocol can be found on the protocol-specific web page (PSWP).

GLOSSARY OF PROTOCOL-SPECIFIC TERMS

BMI	body mass index
CAP	College of American Pathologists
CA-RNA	cell associated HIV-1 RNA
CDC	Centers for Disease Control and Prevention
CKD	chronic kidney disease
CLIA	Clinical Laboratory Improvement Amendments
CpG	cytosine phosphoguanosine
DNA	deoxyribonucleic acid
DVT	deep venous thrombosis
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMT	geometric mean titers
HBcAb	hepatitis B virus core antibody
HBsAb	hepatitis B virus surface antibody
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IM	intramuscular
INR	international normalized ratio
IQA	immunology quality assessment
LRA	latency reversal agent
MAAE	medically attended adverse event
mcg	microgram
MIP1β	macrophage inflammatory protein1β
MOPS	Manual of Procedures
PCR	polymerase chain reaction
PE	pulmonary embolism
PIR	post-injection reaction
PLWH	people living with HIV
RNA-Seq	RNA sequencing
SNP	single-nucleotide polymorphisms
SPR	seroprotection response(s)
TLR9	Toll-like receptor 9
VQA	Virology Quality Assurance

SCHEMA

A5379
B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe):
Evaluation of HEPLISAV-B

DESIGN

A5379 is a phase III/IV, prospective, open-label, interventional, two group study being conducted at both US and non-US sites, with one group (Group A) consisting of a randomized, controlled trial with three study arms and the other group (Group B) consisting of a single arm. The study will involve adults living with HIV with a history of nonresponse to hepatitis B (HBV) vaccination (Group A HBV vaccine-experienced) and adults living with HIV with no known prior history of HBV vaccination (Group B HBV vaccine-naïve). Participants in Group A will be randomized 1:1:1 to receive HEPLISAV-B (Arm 1 [two doses] and Arm 2 [three doses]) or ENGERIX-B (Arm 3 [three doses]). Participants in Group B will receive three doses of HEPLISAV-B.

In Group A, Arms 2 and 3, the first post-entry visit (≥16 to ≤28 hours post first vaccination) is scheduled only for sample collection, and is limited to US sites only. While attendance at this first post-entry visit is strongly encouraged, Group A, Arms 2 and 3, participants may opt out of it at screening.

DURATION

Participants will be on study for 72 weeks.

SAMPLE SIZE

634 participants: 561 in Group A (187 each in Arms 1, 2, and 3) and 73 in Group B.

POPULATION

Adults ≥18 and ≤70 years living with HIV with either prior history of HBV vaccination who failed to achieve protective levels of antibodies against HBV surface antigen (HBsAb <10 mIU/mL, negative, or indeterminate) (Group A) or those who were never vaccinated for HBV (Group B). Participants must be on antiretroviral therapy (ART) for >56 days immediately prior to study entry with an HIV-1 RNA <1000 copies/mL and a CD4+ T-cell count ≥100 cells/mm^3 within 180 days prior to study entry.

Enrollment of women is encouraged, and the study will aim to enroll a minimum of 30% of women in Group A and, separately, in Group B. In Group A, 168 slots will be reserved for women, and in Group B, 22 slots will be reserved for women. Enrollment will be monitored closely, and if determined necessary by the study team and approved by the AIDS Clinical Trials Group (ACTG) Scientific Agenda Steering Committee (SASC), the cap on male participant enrollment may be lifted.

Enrollment at non-US sites is also encouraged, and the study will initially reserve 30% in each group for participants from non-US sites: 168 slots for Group A and 22 slots for Group B. After 9 months from enrollment of the first participant, there will be flexibility for lifting these restrictions if required to ensure that enrollment completion is not delayed.

STRATIFICATION

Randomization in Group A will be stratified by sex assigned at birth (male versus female) and diabetes status (yes versus no). Diabetes is defined as an existing diagnosis of diabetes at screening, screening hemoglobin A1c ≥6.5%, or being treated with insulin or a hypoglycemic agent for a diagnosis of diabetes.

REGIMEN

Participants in Group A will be randomized to receive HEPLISAV-B two doses (Arm 1), HEPLISAV-B three doses (Arm 2), or ENGERIX-B three doses (Arm 3). Participants in Group B will receive HEPLISAV-B three doses. HEPLISAV-B will be administered intramuscularly as 0.5 mL dose (contains 20 micrograms [mcg] of HBsAg and 3000 mcg of cytosine phosphoguanosine [CpG] 1018) at weeks 0, 4, and 24 (except for participants in Group A, Arm 1 [weeks 0 and 4]). ENGERIX-B will be administered intramuscularly as 1 mL dose (contains 20 mcg HBsAg) at weeks 0, 4, and 24.

1.0 HYPOTHESES AND STUDY OBJECTIVES

1.1 Hypotheses

1.1.1 In participants living with HIV, HEPLISAV-B vaccination given as a two-dose series achieves noninferior seroprotection response (SPR) rate compared to standard dose ENGERIX-B.

1.1.2 In participants living with HIV, HEPLISAV-B vaccination given as a three-dose series achieves superior SPR rate compared to standard dose ENGERIX-B.

1.2 Primary Objectives

1.2.1 To compare the week 12 SPR of a two-dose regimen of HEPLISAV-B (Group A, Arm 1) versus the week 28 SPR of a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in hepatitis B virus (HBV) vaccine-experienced participants living with HIV (Group A).

1.2.2 To compare the week 28 SPR of a three-dose regimen of HEPLISAV-B (Group A, Arm 2) versus a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.2.3 To determine the week 28 SPR of a three-dose regimen of HEPLISAV-B in HBV vaccine-naïve participants living with HIV (Group B).

1.2.4 To describe adverse events (AEs) reported in each study arm (Groups A and B, separately) over the duration of the study.

1.3 Secondary Objectives

1.3.1 To compare the week 12 geometric mean titers (GMT) of a two-dose regimen of HEPLISAV-B (Group A, Arm 1) versus the week 28 GMT of a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.2 To compare the week 28 GMT of a three-dose regimen of HEPLISAV-B (Group A, Arm 2) versus a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.3 To compare the SPR and GMT 4, 8, 24, and 48 weeks after last vaccination of a two-dose regimen of HEPLISAV-B (Group A, Arm 1) versus a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.4 To compare the SPR and GMT 8, 24, and 48 weeks after last vaccination of a three-dose regimen of HEPLISAV-B (Group A, Arm 2) versus a standard three-

dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.5 To compare the SPR and GMT 4, 8, 24 and 48 weeks after last vaccination of a two-dose regimen of HEPLISAV-B (Group A, Arm 1) versus a three-dose regimen of HEPLISAV-B (Group A, Arm 2) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.6 To assess SPR and GMT at weeks 4, 8, 12, and 24 between HEPLISAV-B (Group A, Arms 1 and 2 combined) and ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.3.7 To determine the week 28 GMT of a three-dose regimen of HEPLISAV-B in HBV vaccine-naïve participants living with HIV (Group B).

1.3.8 To determine the weeks 32, 48, and 72 SPR and GMT of a three-dose regimen of HEPLISAV-B in HBV vaccine-naïve participants living with HIV (Group B).

1.3.9 To determine the weeks 4, 8, 12, and 24 SPR and GMT with HEPLISAV-B in HBV vaccine-naïve participants living with HIV (Group B).

1.3.10 To describe incidence of Grade ≥2 AEs within 4 weeks of each injection in each study arm (Groups A and B, separately).

1.3.11 To assess host characteristics associated with vaccine response including factors such as age, sex, diabetes, body mass index (BMI), baseline CD4+ T-cell count, and smoking status (Groups A and B, separately).

1.3.12 To compare SPR and GMT at week 72 between HEPLISAV-B two-dose (Group A, Arm 1) and three-dose arms (Group A, Arm 2).

1.4 Exploratory Objectives

1.4.1 To compare SPR and GMT at weeks 4, 8, 12, 24, 28, 32, 48, and 72 with HEPLISAV-B in HBV vaccine-experienced participants (Group A, Arm 2) to HBV vaccine-naïve participants living with HIV (Group B).

1.4.2 To compare HBV surface antigen-specific B and T-cell responses, including cell function and phenotype, at baseline and at weeks 12 and 28 with three doses of HEPLISAV-B (Group A, Arm 2) to a standard three-dose regimen of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.4.3 To compare innate immune soluble factors at baseline and approximately 24 hours after the first dose of HEPLISAV-B (Group A, Arm 2) and the first dose of ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.4.4 To identify specific genes/gene sets via RNA sequencing (RNA-Seq) at approximately 24 hours after vaccination that differ from baseline and adaptive cell phenotypes at weeks 12 and 24 that are associated with SPR and GMT with HEPLISAV-B (Group A, Arm 2) compared to ENGERIX-B (Group A, Arm 3) in HBV vaccine-experienced participants living with HIV (Group A).

1.4.5 To analyze single-nucleotide polymorphisms (SNPs) in TLR-9 and assess their associations with baseline and vaccine-induced responses (Group A, Arms 2 and 3).

1.5 Exploratory Objectives for HIV Reservoir

1.5.1 To evaluate the level of HIV-1 gene expression at baseline and week 28 after injection with HEPLISAV-B (Group A, Arm 2) and ENGERIX-B (Group A, Arm 3) of cell-associated HIV-1 RNA (CA-RNA) in CD4+ T-cells from HBV vaccine-experienced and vaccine-naïve participants living with HIV who have undetectable HIV RNA levels.

1.5.2 To evaluate the impact of HEPLISAV-B (Group A, Arm 2) and ENGERIX-B (Group A, Arm 3) vaccination on intact provirus as measured by a digital droplet polymerase chain reaction (PCR) assay at baseline and week 28.

1.5.3 To assess the impact of HEPLISAV-B (Group A, Arms 1 and 2) and ENGERIX-B (Group A, Arm 3) vaccination on markers of HIV-1 persistence, as measured by total deoxyribonucleic acid (DNA) levels at baseline and week 28.

1.5.4 To measure levels of HIV-specific immunity and activation at baseline and week 28 after HEPLISAV-B (Group A, Arm 2) and ENGERIX-B (Group A, Arm 3) vaccination, including:

- HIV-1-specific immune responses
- T-cell activation
- Expression of exhaustion markers on T-cells

1.5.5 To assess innate cellular markers and soluble factors in relationship to HEPLISAV- B (Group A, Arm 2) and ENGERIX-B (Group A, Arm 3) vaccination or virologic outcome measures.

2.0 INTRODUCTION

2.1 Background

While vaccination is the cornerstone of prevention strategies for HBV, the response to current standard vaccination is suboptimal in those living with HIV. A host of studies document overall response rates, defined as achievement of ≥10 mIU/mL of hepatitis B surface antibody (HBsAb) to range from 30-70% following a standard three-dose series [1, 2]. Several studies have tried to improve these response rates with addition of adjuvants and increases in dose or dose frequency. Most strategies have proved to be ineffective or marginally effective. Some providers utilize an off-label strategy of double-

dose vaccine (40 micrograms [mcg] recombinant HBV surface antigen [HBsAg]) given in four intramuscular (IM) doses. In a key study, this approach increased primary response rates to over 80% vs. 65% for controls receiving a standard three-dose vaccination series [3]. Geometric mean titers were higher using this regimen as well and this response persisted for up to 42 months of follow-up [4]. However, this approach still does not achieve the 95% response rates seen in individuals without HIV. Moreover, it is costly due to the double-dose requirement and often requires individuals to receive two injections at each visit using standard 20 mcg vaccine preparations.

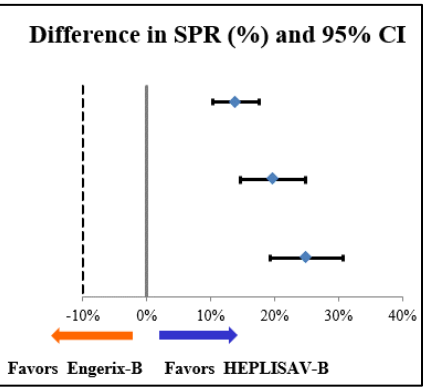
Efforts at repeat vaccination in those who failed a primary vaccination series are also variable. Irungu et al. reported achieving an overall 83% response with two courses of vaccination using 20 mcg dosing x three injections for each series [5]. Others reported lower rates of response following revaccination, even when 40 mcg doses were given for the repeat [6]. The French National Agency for Research on AIDS and Viral Hepatitis (ANRS) conducted a randomized controlled trial of comparing 20 mcg and 40 mcg in rigorously defined non-responders but did not find 40 mcg to achieve superior SPRs. Age, CD4+ count, sex, race, tobacco use/smoking status, BMI, and presence of liver disease are all associated with lack of vaccine efficacy [2, 6, 7].

Recently, a new vaccine for HBV prevention was approved by the United States (US) Food and Drug Administration (FDA). The HEPLISAV-B® vaccine (Dynavax Technologies Corporation) is a 0.5 mL aqueous mixture of the HBsAg (20 mcg) combined with 3 mg of CpG1018, an adjuvant Toll-like receptor 9 (TLR9) agonist. It is given as an IM injection at 0 and 1 months. In pivotal trials this regimen was superior to a three-dose vaccine series of ENGERIX-B, which has been licensed and used for many years in the US and worldwide. Table 2.1-1 below shows a comparison of SPR rates, including in diabetic participants who also have poor HBV vaccine responses. The responses were statistically higher than in control participants in difficult to vaccinate populations. Overall, the vaccine's safety profile matched that of the ENGERIX-B product. A subsequent study involving participants with chronic kidney disease (CKD), another group with low vaccine response rates, compared a 0, 1, and 6 month schedule of HEPLISAV-B to a double-dose ENGERIX-B series of four doses (0, 1, 2, and 6 months) in participants never exposed to HBV or HBV vaccination. For the primary endpoint, 89.5% achieved seroprotection at week 28 with HEPLISAV-B three doses compared to 81.3% with ENGERIX-B four double doses. In addition, superior peak immune responses, earlier seroprotection, and more persistent seroprotection were observed in the HEPLISAV-B arm. Of relevance to the A5379 study design, a third dose of HEPLISAV-B appeared to be important in this "difficult to vaccinate" population since SPR in the HEPLISAV-B group at week 12 (after two doses) was 64.3% compared to 89.5% achieved after three doses [8]. Another randomized study compared a booster dose of HEPLISAV-B to ENGERIX-B and Fendrix (HBV vaccine indicated for individuals with renal insufficiency) in adults on hemodialysis with prior HBV vaccine but without current seroprotection (categorized as either prior non-responders or prior responders). At week 4, after dosing in prior non-responders, the SPR in the HEPLISAV-B group (16 of 38 participants; 42.1%) was higher than the SPR in the ENGERIX-B group (7 of 37 participants; 18.9%) and the Fendrix group (12 of 41 participants; 29.3%). At week 4, after dosing in prior responders, the SPR in the HEPLISAV-B group was 80.0% (12 of 15

participants), in the ENGERIX-B group was 90.9% (10 of 11 participants), and in the Fendrix group was 100% (10 of 10 participants) [Dynavax, Data on File].

Table 2.1-1: Comparison of SPR Rates

Study Number	HEPLISAV-B SPR (%)	HEPLISAV-B N	Engerix-B SPR (%)	Engerix-B N	Difference in SPR (95% CI)
HBV-10	95.0	1,511	81.3	521	13.7 (10.4, 17.5)
HBV-16	90.1	1,121	70.5	353	19.6 (14.7, 24.8)
HBV-23	90.0	640	65.1	321	24.9 (19.3, 30.7)



In addition, a small prior pilot study conducted in people living with HIV (PLWH) (one-half of whom had experienced previous vaccination failure), utilizing a combination of ENGERIX-B with or without a different TLR-9 agonist, supports that TLR-9 agonist may also augment response in PLWH. In this study, which utilized a three-dose vaccine schedule of 0, 1, and 2 months, seroprotective titres were found in 19/19 (100%) of participants receiving CPG 7909 compared to 12/19 (63%) receiving ENGERIX-B (P = 0.008) [9]. In follow up extending to 60 months, the participants who received the TLR-9 agonist had statistically significantly higher seroprotection rates and GMTs as well [10].

The proposed study will compare the efficacy and safety of HEPLISAV-B and ENGERIX-B in a population of HBV vaccine non-responders living with HIV.

HEPLISAV-B is only approved for use in adults 18 years of age and older [HEPLISAV-B® Package Insert, 2018]. Therefore, this study will not allow enrollment of participants under the age of 18 years. Participants, regardless of age, will receive ENGERIX-B 1 mL dose if they are randomized to the ENGERIX-B Arm 3 as done in prior HEPLISAV-B studies.

Before it was approved by the FDA, HEPLISAV-B was tested in more than 9500 people. Overall, the side effects were similar to the side effects seen with other vaccines. In a single study (HBV-23), people who got HEPLISAV-B had myocardial infarctions more often than people who got ENGERIX-B (0.17% [n = 16] vs. 0.05% [n = 2]). In a further study, no causal relationship between HEPLISAV-B and myocardial infarction was found [11]. After FDA approval, Dynavax, the manufacturer of HEPLISAV-B, began conducting a large observational study of 30,000 people who received HEPLISAV-B and 30,000 people who received ENGERIX-B to evaluate myocardial infarctions and the theoretical concern that vaccines can cause autoimmune disease. **The study** showed no relationship between HEPLISAV-B and myocardial infarctions. **Of 31,183 recipients of HepB-CpG vaccine and 38,442 recipients of HepB-alum vaccine, rates of acute MI per 1000 person-years were 1.67 and 1.86, respectively [12].** One of the primary objectives of A5379 is to assess safety of the vaccine in PLWH.

There are no clinical studies of HEPLISAV-B in **participants who are** pregnant. Developmental toxicity studies done on female rats did not reveal any harm to the fetus due to this vaccine formulation. No AEs were observed on both pre and post-natal development up to the time of weaning. Current available human data on HEPLISAV-B administration in **people who are** pregnant are inadequate to inform vaccine-associated risks in pregnancy [HEPLISAV-B® Package Insert, 2018]. On account of lack of data on safety in pregnancy and the significantly low likelihood of obtaining evaluable data on pregnancy, this study will not enroll **people who are** pregnant. International Ethical Guidelines for Health-related Research Involving Humans (2016) require underrepresented groups, such as **people who are** pregnant, be provided access to research. Participants living with HIV are considered at risk for HBV, and pregnancy could further increase that risk on account of its impact on the immune system. Non-responders to available HBV vaccines and who are living with HIV, currently have no good options for HBV vaccination. To ensure participants have the opportunity to achieve the best possible clinical outcomes, **participants** who become pregnant while on the study vaccine series will have the option to complete their scheduled vaccination series and continue on study. Both ENGERIX-B and HEPLISAV-B are FDA-approved marketed products. ENGERIX-B has been widely used in pregnancy, and registry information does not suggest any additional pregnancy-related risks [ENGERIX-B® Package Insert, 2018]. **Participants** who decide to continue on the study will be counseled on the potential unknown pregnancy-related risks of HEPLISAV-B due to the lack of adequate safety and efficacy data in humans. Such participants would need to complete a pregnancy-specific informed consent process. Participants who decide to stay on their vaccination series and participants who stop the series will continue evaluations on study per the schedule of evaluations (SOE).

There are no data to inform on the excretion of HEPLISAV-B in human breast milk. It is not known what impact HEPLISAV-B could have on the breastfed infant or on milk production and excretion by the mother [HEPLISAV-B® Package Insert, 2018]. Therefore, **people** breastfeeding will not be enrolled.

2.2 Rationale

Hepatitis B vaccination response to standard regimens is suboptimal in persons living with HIV. A variety of modalities to improve response (primary or secondary series) have been utilized but none have gained universal acceptance. Though many factors influence primary and secondary responses to vaccination (age, sex, CD4+ count, race, tobacco use, prior exposures, body weight, comorbidities such as diabetes and liver disease), the “real-world” presentation of **PLWH** without protective HBsAb titers (≥10 mIU/mL) represents a decision point for clinicians. Key care outcomes include achievement of protective antibody levels with the minimum number of doses, the least number of total injections, and the best durability of response. To address these issues, the proposed trial will evaluate a two- and three-dose regimen of HEPLISAV-B, each compared to a standard three-dose regimen of ENGERIX-B in HBV vaccine-experienced participants with HBsAb <10 mIU/mL. The specific rationale for having a three-arm study is summarized below:

- The rate of response to either two or three doses of HEPLISAV-B in this population is difficult to estimate with precision.
- Though arguments can be made for and against a strong response in the two-dose arm (e.g., most participants will have higher CD4+ levels), it is possible that the three-dose arm may be required to achieve acceptable rates of SPR.
- If the two-dose arm is found to be non-inferior this would likely become a preferred regimen for PLWH.
- Failure to achieve SPR in the two-dose arm does not predict response in the three-dose arm, which was more effective in a dialysis population.

We will stratify by sex assigned at birth (male versus female) and presence or absence of diabetes, and we will compare efficacy of two and three doses of HEPLISAV-B, each compared to ENGERIX-B in HBV vaccine-experienced participants (Group A). There is considerable variability in reports of SPR among those living with HIV. We have selected a 70% response rate in the ENGERIX-B control. The response estimates come from prior studies documented above and accounts for the possibility that some persons may not have received full series or may be prior responders with waned immunity. (Thus higher response rates are expected in nonresponders than vaccine naïve participants in this study) [**13**]. The three-dose HEPLISAV-B arm will be compared to the ENGERIX-B control and assessed for superiority, at week 28, with an estimate of an 85% response rate selected for HEPLISAV-B based on the differential in SPR rates in the HEPLISAV-B studies described above. The two-dose HEPLISAV-B arm will be assessed for non-inferiority to ENGERIX-B control using the same primary endpoints (week 12 SPR for HEPLISAV-B, week 28 SPR for ENGERIX-B) and noninferiority margin of 10% as used in Dynavax registrational trials of HEPLISAV-B (HBV-10, HBV-16). A non-inferiority comparison was chosen as most appropriate because of the advantages a two-dose schedule offers in terms of cost, convenience, and completion rates. For this study the HEPLISAV-B two-dose week 12 response was conservatively estimated at 75%. Week 12 is used (rather than week 8) because prior studies demonstrated that HEPLISAV-B two-dose SPR rises over time due to the TLR9 agonist effect (e.g., SPR 8 weeks after vaccination is greater than 4 weeks after vaccination). For three-dose arms, a consistent time point of week 28 was recommended by the US FDA for both HEPLISAV-B and ENGERIX-B; however, it is still anticipated that the SPR will increase over time in participants that receive HEPLISAV-B, so later endpoints will be examined in secondary analyses. Secondary analyses will focus on the SPR rates over time, HBV surface antibody (HBsAb) titers achieved, and other predictors of response in these participants including known variables that have been shown to affect vaccine response in other studies.

The rationale for testing a small group of HBV vaccine-naïve participants is also derived from US FDA guidance regarding the need for development of a point estimate for SPR in this group. In HBV vaccine-naïve participants living with HIV, we will evaluate the vaccine efficacy compared to historical response rates. These rates range from 35-70% in the literature, and we aim to show that response to HEPLISAV-B among HBV vaccine-naïve participants living with HIV will be greater than 55%. A prior ACTG study, A5220, provides rationale for choosing 55% as the response rate. A5220 was a two-arm, randomized ACTG study completed in 2008 to evaluate the efficacy and safety of

vaccinating participants **living with HIV** using HBV vaccine (40 mcg, Recombivax) at weeks 0, 4, and 12 with or without GM-CSF as an adjuvant. The study population consisted of participants naïve to HBV vaccination, ≥18 years of age, CD4+ cell count ≥200 cells/mm^3, and seronegative for HBV and HCV. The study enrolled 48 participants and concluded that GM-CSF did not have an effect: 65% without GM-CSF and 52% (with GM-CSF), 59% overall (95% CI, 43%, 73%).

Exploratory Immunology Aims

The BEe-HIVe trial hypothesis (refer to section 1.1.2) is that HEPLISAV-B vaccination (HBsAg with cytosine phosphoguanosine [CpG] 1018) in participants living with HIV achieves superior SPR rates compared to standard dose ENGERIX-B (HBsAg with alum). If correct, HEPLISAV-B vaccination will induce more robust immune responses than ENGERIX-B. Given that SPR is a measure of induction of antibodies against HBsAg, and that CD4+ T-cells are required to produce high affinity, robust antibody responses, CpG 1018 is therefore predicted to enhance HBV-specific CD4+ T function [**14**]. Antibodies are produced by B cells and plasma cells, which differentiate from B cells [**14**]. Thus, characterization of B cells specific for HBsAg is critical to understanding the generation of effective antibodies. Responses induced through HEPLISAV-B vaccination that differ from those induced by ENGERIX-B vaccination have high potential to identify 1) pathways critical to induction of robust antibody responses to inform rational vaccine design and 2) pathways impaired in HIV infection, activation of which requires more robust stimulation (CpG versus alum) to overcome HIV-specific impairment.

HIV cure/eradication strategies have included a variety of latency reversal strategies, including TLR9 agonist treatment. The adjuvant in HEPLISAV-B, CpG 1018 is a TLR9 agonist and its mechanism of action has been shown to require TLR9 activation [**15**]. Previous studies, including a study of a different CpG TLR9 agonist administered as part of a pneumococcal vaccine regimen, have shown that TLR9 activation in HIV infection increases HIV-1 transcription and reduces proviral DNA, key outcomes in HIV-1 eradication therapy. These changes in the HIV reservoir occurred in association with enhanced cellular immunity [**16**, **17**]. Thus, a thorough assessment of the HIV reservoir and immune responses before and after vaccination with HEPLISAV-B could determine whether CpG 1018 might serve as a latency reversal agent (LRA), and, if so, its mechanism of action as an LRA. This has the potential to highlight pathways of immune activation critical to latency reversal.

3.0 STUDY DESIGN

A5379 is a phase III/IV, prospective, open-label, interventional, two-group study, enrolling concurrently, with one group (Group A) consisting of a randomized, controlled trial with three study arms and the other group (Group B) consisting of a single study arm. The study will be conducted at both US and non-US sites. The study will involve adults living with HIV with prior history of HBV vaccination who do not have antibodies against HBsAg at protective levels (HBsAb <10 mIU/mL, negative, or indeterminate) (Group A non-responders) and adults living with HIV with no known prior history of HBV vaccination (Group B HBV vaccine-naïve). Participants in Group A will be randomized

1:1:1 to receive HEPLISAV-B (Arms 1 and 2) or ENGERIX-B (Arm 3). Arm 3 (ENGERIX-B) will serve as the control arm for both Arms 1 and 2. Participants in Group B will receive HEPLISAV-B. The target sample size is 634 participants: 561 in Group A (187 each in Arms 1, 2, and 3) and 73 in Group B. The participant enrollment target for women is at least 30% in each study group. Enrollment at non-US sites is encouraged (refer to Schema for further details about the non-US and women participant enrollment plan). Participants will be on study for 72 weeks. Randomization in Group A will be stratified by sex assigned at birth and diabetes (refer to Schema for the definition).

HEPLISAV-B will be administered intramuscularly as 0.5 mL dose (contains 20 mcg of HBsAg and 3000 mcg of CpG 1018) at:

- Weeks 0 and 4 for all participants in Group A, Arm 1;
- Weeks 0, 4, and 24 for all participants in Group A, Arm 2; and
- Weeks 0, 4, and 24 for all participants in Group B.

ENGERIX-B will be administered intramuscularly as 1 mL dose (contains 20 mcg HBsAg) at weeks 0, 4, and 24 for all participants in Group A, Arm 3.

Group A
Group A (non-responders) will include participants living with HIV with a history of HBV vaccination who do not have HBsAb at protective levels (HBsAb <10 mIU/mL, negative, or indeterminate). Participants in Group A will be randomized 1:1:1 to receive HEPLISAV-B two doses (Arm 1), HEPLISAV-B three doses (Arm 2), or ENGERIX-B three doses (Arm 3). The primary outcome for Group A will be percent of participants with ≥10 mIU/mL HBsAb measured at week 12 for Arm 1 and week 28 for Arms 2 and 3. Refer to the SOE for seroprotection rate assessment time points.

Group B
Group B (HBV vaccine-naïve) will include participants living with HIV who have no prior known history of receiving HBV vaccination. The primary outcome for Group B will be SPR 4 weeks after the vaccination series (week 28), and we will examine if SPR proportion is greater than 55%. Refer to the SOE for seroprotection rate assessment time points.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria, Groups A and B

NOTE: See sections 4.2 and 4.3 for inclusion criteria specific to Group A and Group B, respectively.

4.1.1 HIV-1 infection, documented by:

- **A**ny licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit at any time prior to study entry
  AND

- Confirmed by **one of the following:**
  - A licensed Western blot
  - A second antibody test by a method other than the initial rapid HIV and/or E/CIA
  - HIV-1 antigen**, or**
  - Plasma HIV-1 RNA viral load

NOTE: The term "licensed" refers to a US FDA-approved kit, which is required for all IND studies, or for sites located in countries other than the US, a kit that has been certified or licensed by an oversight body within that country and validated internally. Non-US sites are encouraged to use US FDA-approved methods for IND studies.

The **Council for International Organizations of Medical Sciences/**World Health Organization [**18**] and Centers for Disease Control and Prevention (CDC) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

4.1.2 On HIV-1 antiretroviral therapy (ART) for >56 days immediately prior to study entry.

NOTE: **Changes to ART due to ART toxicity in the 28 days prior to study entry are not allowed. For questions related to ART toxicity, sites should contact the team per the Study Management section.**

4.1.3 CD4+ T-cell count ≥100 cells/mm^3 obtained within 180 days prior to study entry at any US laboratory that has a Clinical Laboratory Improvement Amendments (CLIA) certification or its equivalent, or at any network-approved non-US laboratory that is **DAIDS** Immunology Quality Assessment (IQA) certified.

NOTE: If multiple results are available within 180 days prior to study entry, use most recent result.

4.1.4 HIV-1 RNA <1000 copies/mL obtained within 180 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that is Virology Quality Assurance (VQA) certified.

NOTE: If multiple results are available within 180 days prior to study entry, use most recent result.

4.1.5 The following laboratory values obtained within 45 days prior to study entry by any US laboratory that has a CLIA certification or its equivalent, or at any network-approved non-US laboratory that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

- Hemoglobin ≥9 g/dL for men and ≥8 g/dL for women.
  - NOTE: Men and women are defined by sex assigned at birth for this study.
- International normalized ratio (INR) ≤1.5 x ULN, except for individuals with known hemophilia or a stable anticoagulant regimen affecting INR.
- Albumin ≥3 g/dL
- Aspartate aminotransferase (AST) (SGOT) ≤2.5 × ULN
- Alanine aminotransferase (ALT) (SGPT) ≤2.5 × ULN
- Hemoglobin A1c <9.0%

4.1.6 For individuals of reproductive potential who can become pregnant, a negative serum or urine pregnancy test (urine test must have a sensitivity of <25 mIU/mL) within 2 days prior to study entry by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care (POC)/CLIA-waived test, or at any network-approved non-US laboratory or clinic that operates in accordance with GCLP and participates in appropriate external quality assurance programs.

NOTE A: Individuals of reproductive potential are defined as those who have reached menarche and who have not been post-menopausal for at least 24 consecutive months (i.e., have had menses within the preceding 24 months), and have not undergone surgical sterilization such as hysterectomy, bilateral oophorectomy, tubal ligation, or salpingectomy.

NOTE B: Individual report is considered acceptable documentation of reproductive status.

4.1.7 If participating in sexual activity that could lead to pregnancy, individuals of reproductive potential who can become pregnant must agree to use contraception throughout the study. At least one of the following must be used throughout the study:
- Condom (male or female) with or without spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

4.1.8 Adequate venous access for the purpose of phlebotomy.

4.1.9 Age ≥18 and ≤70 years.

4.1.10 Ability and willingness of individual or, if the individual lacks decision-making capacity, their legal guardian/representative to provide informed consent.

4.1.11 Willingness to be contacted by telephone, text message, or e-mail by study staff throughout the study.

4.2 Inclusion Criteria, Group A only

4.2.1 Serum Hepatitis B antibody <10 mIU/mL, non-reactive (negative), or indeterminate as determined by a CLIA- or College of American Pathologists (CAP)-certified or equivalent laboratory within 45 days prior to study entry.

NOTE A: If a mIU/mL value is given, the decision should be made on the value. For example, if a value of ≥10 mIU/mL is given and also reported as indeterminate, the individual would be considered ineligible based on the numeric report.

NOTE B: Refer to table on the protocol-specific web page (PSWP) for further details.

4.2.2 Documentation of HBV vaccination >168 days prior to study entry.

NOTE A: Completion of the vaccination series is not required.

NOTE B: Multiple past vaccination series are permitted.

NOTE C: Documentation of combination HBV vaccinations (e.g., Twinrix) are acceptable.

4.3 Inclusion Criterion, Group B only

4.3.1 Serum Hepatitis B antibody non-reactive (negative) as determined by a CLIA- or CAP-certified or equivalent laboratory within 45 days prior to study entry.

4.4 Exclusion Criteria, Groups A and B

NOTE: See sections 4.5 and 4.6 for exclusion criteria specific to Group A and Group B, respectively.

4.4.1 Infection or prior exposure to HBV defined as HBsAg positive or HBV core antibody (HBcAb) positive any time prior to or at screening.

NOTE A: Individuals with any documented history of HBcAb positive or HBsAg positive should not undergo testing at screening because even if results at screening are negative, they are ineligible.

NOTE B: Individuals without documented history or with history of HBcAb negative or HBsAg negative results will have HBcAb and HBsAg testing performed at screening to determine eligibility.

4.4.2 Serum HBsAb level ≥10 mIU/mL or positive at screening or any other time prior to screening.

4.4.3 Presence of any active or acute AIDS-defining opportunistic infections within 45 days prior to study entry.

NOTE: A list of AIDS-defining opportunistic infections is located on the PSWP.

4.4.4 History of solid organ transplantation.

4.4.5 Current or prior history of clinical hepatic decompensation (e.g., ascites, encephalopathy, or variceal hemorrhage).

4.4.6 Diagnosis of chronic kidney disease (CKD) stage G4 (estimated glomerular filtration rate [eGFR] of 15-29 mL/min) or CKD stage G5 also referred to as End-Stage Renal Disease (eGFR of <15 mL/min).

NOTE: The Cockcroft-Gault formula located on the A5379 PSWP can be used to calculate creatinine clearance as an estimate of eGFR.

4.4.7 Cancer diagnosis within 5 years prior to study entry, other than squamous or basal cell carcinoma of the skin **and/or resolved or inactive cutaneous Kaposi sarcoma**.

4.4.8 Currently receiving chemotherapy.

4.4.9 Chronic use and/or receipt of the following within 45 days prior to study entry: systemically administered immunosuppressive agents (e.g., prednisone equivalent >10 mg/day, systemic corticosteroids [more than 3 consecutive days]) or other immunomodulators, with the exception of inhaled steroids.

4.4.10 Currently breastfeeding.

4.4.11 Individuals who plan to become pregnant during the study.

4.4.12 Plan to discontinue ART during the study.

4.4.13 Known allergy/sensitivity or any hypersensitivity to any HBV vaccine or yeast.

4.4.14 Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.

4.4.15 Active, serious infection (other than HIV-1 or hepatitis C virus [HCV]) requiring parenteral antibiotics, antivirals, or antifungals within 45 days prior to study entry.

4.4.16 Receipt of any inactivated virus vaccine**, non-replicating vaccine (including live), or mRNA vaccine**, within 14 days prior to study entry.

NOTE: Receipt of flu vaccine within 14 days prior to study entry is allowed.

4.4.17 Receipt of any of the following within 45 days prior to study entry:

- Live, **replicating** virus vaccine
- Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Any other investigational medicinal agent

4.4.18 Receipt of immunoglobulin or blood products within 90 days prior to study entry.

4.4.19 Receipt of an injection of DNA plasmids or oligonucleotides within 60 days prior to study entry.

4.5 Exclusion Criteria, Group A only

4.5.1 Hepatitis B virus vaccination ≤168 days prior to study entry.

4.5.2 Receipt of HEPLISAV-B vaccine at any time prior to study entry.

4.6 Exclusion Criterion, Group B only

4.6.1 Known HBV vaccination prior to study entry.

4.7 Study Enrollment Procedures

4.7.1 Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by the institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE) responsible for oversight of the study. Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) WILL be reviewed and approved by the DAIDS PRO, and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approvals for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all required documents have been received. Site-specific ICF(s)

WILL NOT be reviewed and approved by the DAIDS PRO, and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

Once a candidate for study entry has been identified, details will be carefully discussed with the participant. The participant (or, when necessary, the legal representative if the participant is under guardianship) will be asked to read and sign the approved protocol consent form.
Participants from whom a signed informed consent has been obtained may be screened and enrolled, if they qualify. An ACTG Screening Checklist must be entered through the DMC **Study** Enrollment System.

4.7.2 Protocol Activation

Prior to enrollment, sites must complete the Protocol Activation Checklist found on the ACTG Member website. This checklist must be approved prior to any screening of participants for enrollment.

4.7.3 Randomization/Participant Registration

For participants from whom informed consent has been obtained, but who are deemed ineligible or who do not enroll into the initial protocol step, an ACTG Screening Failure Results form must be keyed into the database.

Participants who meet the enrollment criteria will be registered or randomized to the study according to standard ACTG DMC procedures.

4.8 Co-enrollment Guidelines

United States sites are encouraged to co-enroll participants in A5128, “Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.” Co-enrollment in A5128 does not require permission from the A5379 protocol chairs.

Non-US sites are encouraged to co-enroll participants in A5243, “Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.” Co-enrollment in A5243 does not require permission from the A5379 protocol chairs.

Individuals who consent to these additional studies would have additional blood drawn for these studies. Participants must be made aware that they can schedule this additional blood draw if they feel the need to do that.

For specific questions and approval for co-enrollment in other studies, sites should first check the PSWP or contact the protocol team via e-mail as described in the Study Management section.

5.0 STUDY TREATMENT

Study treatment is defined as study-provided HEPLISAV-B or ENGERIX-B.

5.1 Study Product Formulations

5.1.1 HEPLISAV-B

Hepatitis B Vaccine (Recombinant) adjuvanted, 0.5 mL dose contains 20 mcg of HBsAg and 3000 mcg of CpG 1018. HEPLISAV-B is a clear to slightly opalescent, colorless to slightly yellow solution available in vials and prefilled syringes as a sterile solution for intramuscular injection. It should be stored in a refrigerator at 2°C to 8°C (35°F to 46°F) and should not be frozen. Do not administer if product has been frozen.

5.1.2 ENGERIX-B

Hepatitis B Vaccine (Recombinant), 1 mL dose contains 20 mcg HBsAg. ENGERIX-B is a sterile, homogeneous, turbid, white suspension available in two presentations, as single-dose vials and prefilled syringes for intramuscular injection. ENGERIX-B is stored refrigerated between 2° and 8°C (35° and 46°F) and should not be frozen. Do not administer if product has been frozen.

5.2 Regimens, Administration, and Duration

At entry, Group A participants will be randomized 1:1:1 to Arms 1, 2, and 3 as follows:

Arm 1: HEPLISAV-B, 0.5 mL dose administered intramuscularly at weeks 0 and 4.

Arm 2: HEPLISAV-B, 0.5 mL dose administered intramuscularly at weeks 0, 4, and 24.

Arm 3: ENGERIX-B, 1 mL dose administered intramuscularly at weeks 0, 4, and 24.

Group B participants will receive HEPLISAV-B intramuscularly as 0.5 mL dose at weeks 0, 4, and 24.

Participants should remain on their non-study-provided ART throughout the study (72 weeks).

Table 5.2-1: Dosing

Group A	Week 0	Week 4	Week 24
Arm 1	HEPLISAV-B 0.5 mL dose IM	HEPLISAV-B 0.5 mL dose IM	-
Arm 2	HEPLISAV-B 0.5 mL dose IM	HEPLISAV-B 0.5 mL dose IM	HEPLISAV-B 0.5 mL dose IM
Arm 3	ENGERIX-B 1 mL dose IM	ENGERIX-B 1 mL dose IM	ENGERIX-B 1 mL dose IM
Group B	Week 0	Week 4	Week 24
All Participants	HEPLISAV-B 0.5 mL dose IM	HEPLISAV-B 0.5mL dose IM	HEPLISAV-B 0.5 mL dose IM

5.3 Study Product and Preparation for Administration

5.3.1 HEPLISAV-B

1. HEPLISAV-B should be inspected visually for particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
2. The injection site on the arm to be used for immunization will be gently rubbed with an alcohol pad to disinfect the site.
3. The center seals of the vials will be removed, and the vial stoppers wiped with an alcohol wipe prior to insertion of a sterile needle attached to a sterile syringe. The study **staff** will determine the needle size depending upon the participant's deltoid muscle size.
4. Use a sterile needle and sterile syringe to withdraw the vaccine dose from the vial prior to intramuscular injection. Administer within 4 hours of drawing up dose in a syringe. HEPLISAV-B can be kept at room temperature (20°C - 25°C) for up to 8 hours but exposure time to room temperature should be minimized. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated.
5. For the prefilled syringes, attach a sterile needle and administer intramuscularly. The study **staff** will determine the needle size depending upon the participant's deltoid muscle size. HEPLISAV-B should be administered as soon as possible. HEPLISAV-B can be kept at room temperature (20°C-25°C) for up to 8 hours but exposure time to room temperature should be minimized.
6. Administer HEPLISAV-B by intramuscular injection in the deltoid region.

5.3.2 ENGERIX-B

1. Shake well before use and inspect visually for particulate matter and discoloration prior to administration. If either of these conditions exists, the vaccine should not be administered.
2. The injection site on the arm to be used for immunization will be gently rubbed with an alcohol pad to disinfect the site.
3. For the vials, remove the center seals of the vials and wipe the vial stoppers with an alcohol wipe prior to insertion of a sterile needle attached to a sterile syringe. The study **staff** will determine the needle size depending upon the participant's deltoid muscle size.
4. Use a sterile needle and sterile syringe to withdraw the vaccine dose from the vial prior to intramuscular injection. Administer within 4 hours of drawing up dose in a syringe. ENGERIX-B can be kept at room temperature (20°C-25°C) for up to 72 hours but exposure time to room temperature should be minimized. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary unless the needle has been damaged or contaminated.
5. For the prefilled syringes, attach a sterile needle and administer intramuscularly. The study **staff** will determine the needle size depending upon the participant's deltoid muscle size. ENGERIX-B should be administered as soon as possible. ENGERIX-B can be kept at room temperature (20°C-25°C) for up to 72 hours but exposure time to room temperature should be minimized.
6. Administer ENGERIX-B by intramuscular injection in the deltoid region.

5.4 Pharmacy: Product Supply, Distribution, and Accountability

5.4.1 Study Product Acquisition/Distribution

HEPLISAV-B® (Dynavax Technologies Corporation) will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

For sites that ENGERIX-B® will be centrally distributed to from the CRPMC, the site pharmacist should obtain the study product(s) for this protocol by following the instructions in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.*

ENGERIX-B® (GlaxoSmithKline Biologicals) will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC) to all US sites, as well as non-US sites that the vaccine can be distributed to by the CRPMC.

For non-US sites that are unable to receive ENGERIX-B® from the CRPMC due to importation documentation limitation, the vaccine will be locally sourced. Any study product not provided by the study must comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the US in NIAID (DAIDS)-supported and/or -sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf.

5.4.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC and subsequently dispensed. At US clinical research sites (CRSs), all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

5.5 Concomitant Medications

Whenever a concomitant medication or study agent is initiated or a dose changed, investigators must review the concomitant medication's and study agent's most recent package insert, Investigator's Brochure, or updated information from DAIDS to obtain the most current information on drug interactions, contraindications, and precautions.

Additional drug information may be found on the ACTG Precautionary and Prohibited Medications Database located at http://tprc.pharm.buffalo.edu/home/di_search/.

5.5.1 Required Medications

All participants should continue their current ART regimen for the duration of the study. Changes in ART are discouraged during the study, but are allowed if clinical need arises as determined by sites and the participant's treating provider. Sites must report all ART changes on the eCRF on the next study visit following the change in therapy. Antiretroviral therapy will not be provided by the study.

5.5.2 Prohibited Medications

HBV vaccine preparations other than study vaccines HEPLISAV-B and ENGERIX-B **are prohibited.** Standard-of-care (SOC) vaccines, **including COVID-19 vaccines**, will be permitted during the conduct of this study. **If administration of a COVID-19 vaccine occurs after study entry and near the second or third study vaccine dose, adjust the second or third dose of the study vaccine to avoid immediate overlap reactogenicity; however, it is not prohibited to give them together, and this is at the discretion of the site**

investigator. If an SOC vaccine **and/or COVID-19 vaccine** is administered on the same day as the study-provided vaccine, use different arms. **Refer to the A5379 PSWP for further details about COVID-19 vaccines and this study.**

5.5.3 Precautionary Medications

There are no precautionary medications.

6.0 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

Table 6.1-1: Group A (Arm 1 only)

Evaluations	Screening	Entry (Day 0)	Post-Entry Evaluations (Weeks)							Premature Study Discontinuation Evaluations (*refer to section 6.2.4)
			4	8	12	24	28	52	72	
Visit Windows	*Within 45 days*	*≥24 hours after screening*	*-4/+7 days*	*±7 days*				*±14 days*		
Documentation of HIV-1	X									
Medical History	X	X								
Medication History	X	X								
Complete Physical Examination	**X**									
Targeted Physical Examination		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Respiration Rate	**X**	**X**	**X**							
Height		**X**								
Weight		**X**								
Tobacco Use		**X**								
Concomitant Medications			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment Modifications		**X**	**X**							
Hematology	X	X	X	X			X			X*
Liver Function Tests	X	X	X	X			X			X*
INR	X									
Chemistry	X	X					X			X*
Hemoglobin A1c	X									
Pregnancy Testing **(within 2 days prior to the participant receiving HEPLISAV-B)**		X	X						X	X
CD4+/CD8+	X	X					X			X*
HBsAg Qualitative and HBcAb Total	X									
Serum for HBsAb	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X						X			X*
Vaccine Administration HEPLISAV-B		X	X							
Post-vaccination Assessment		X	X							
Diary Card (D= distributed; C= collected)		X^{D}	$X^{D,C}$	X^{C}						
Remote Contact (refer to section 6.3.12 for contact window)		X	X	X						

Table 6.1-2: Group A (Arms 2 and 3 only)

Evaluations	Screening	Entry (Day 0)	Post-Entry Evaluation	Post-Entry Evaluations (Weeks)								Premature Study Discontinuation Evaluations (*refer to section 6.2.4)
				4	8	12	24	28	32	48	72	
Visit Windows	*Within 45 days*	*≥24 hours after screening*	*≥16 to ≤28 hours post 1st vaccination; at US sites only and is optional*	*-4/+7 days*	*±7 days*					*±14 days*		
Documentation of HIV-1	X											
Medical History	X	X										
Medication History	X	X										
Complete Physical Examination	**X**											
Targeted Physical Examination		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Respiration Rate	**X**	**X**		**X**			**X**					
Height		**X**										
Weight		**X**										
Tobacco Use		**X**										
Concomitant Medications				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment Modifications		**X**		**X**			**X**					
Hematology	X	X		X	X			X				X*
Liver Function Tests	X	X		X	X			X				X*
INR	X											
Chemistry	X	X						X				X*
Hemoglobin A1c	X											
Pregnancy Testing **(within 2 days prior to the participant receiving HEPLISAV-B or ENGERIX-B)**		X		X			X				X	X
CD4+/CD8+	X	X						X				X*
HBsAg Qualitative and HBcAb Total	X											
Serum for HBsAb	X	X		X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X	X						X				X*
Stored Plasma and PBMC for Immunologic & Latency Testing		X	X	X		X	X	X		X		X*
Stored PBMC for Genetic Testing						X						
Vaccine Administration		X		X			X					

HEPLISAV-B (Group A Arm 2)												
Vaccine Administration ENGERIX-B (Group A Arm 3)		X		X			X					
Post-vaccination Assessment		X		X			X					
Diary Card (D= distributed; C= collected)		X^{D}		$X^{D,C}$	X^{C}		X^{D}	X^{C}				
Remote Contact (refer to section 6.3.12 for contact window)		X		X	X		X	X				

Table 6.1-3: Group B Only

Evaluations	Screening	Entry (Day 0)	Post-Entry Evaluations (Weeks)								Premature Study Discontinuation Evaluations (*refer to section 6.2.4)
			4	8	12	24	28	32	48	72	
Visit Windows	*Within 45 days*	*≥24 hours after screening*	*-4/+7 days*	*±7 days*					*±14 days*		
Documentation of HIV-1	X										
Medical History	X	X									
Medication History	X	X									
Complete Physical Examination	**X**										
Targeted Physical Examination		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Respiration Rate	**X**	**X**	**X**			**X**					
Height		**X**									
Weight		**X**									
Tobacco Use		**X**									
Concomitant Medications			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Study Treatment Modifications		**X**	**X**			**X**					
Hematology	X	X	X	X			X				X*
Liver Function Tests	X	X	X	X			X				X*
INR	X										
Chemistry	X	X					X				X*
Hemoglobin A1c	X										
Pregnancy Testing **(within 2 days prior to the participant receiving HEPLISAV-B)**		X	X			X				X	X
CD4+/CD8+	X	X					X				X*
HBsAg Qualitative and HBcAb Total	X										
Serum for HBsAb	X	X	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA	X						X				X*
Vaccine Administration HEPLISAV-B		X	X			X					
Post-vaccination Assessment		X	X			X					
Diary Card (D= distributed; C= collected)		X^{D}	$X^{D,C}$	X^{C}		X^{D}	X^{C}				

Remote Contact (refer to section 6.3.12 for contact window)		X	X	X		X	X				

6.2 Timing of Evaluations

6.2.1 Screening Evaluations

Screening evaluations must occur prior to the participant starting any study treatments.

Screening
Screening evaluations to determine eligibility must be completed within 45 days prior to study entry unless otherwise specified.

In addition to data being collected on participants who enroll into the study, demographic, clinical, and laboratory data on screening failures will be captured in a Screening Failure Results form and entered into the ACTG database.

6.2.2 Entry Evaluations

Entry evaluations must occur at least 24 hours after screening evaluations unless otherwise specified. Participants must begin the study vaccine series within 72 hours after registration/randomization.

6.2.3 Post-Entry Evaluations

At US sites, participants in Arms 2 and 3 in Group A are strongly encouraged to return to the clinic for a blood collection between 16 and 28 hours after the first vaccine administration. This visit should occur in the morning to account for peripheral blood mononuclear cell (PBMC) processing. Note that this visit is encouraged; however, participants may opt out at screening. This visit will not be conducted at non-US sites.

Group A, Arm 1, evaluations at week 4 must occur -4/+7 days of the visit, weeks 8 through 28 must occur ±7 days of the visit, and after 28 weeks must occur ±14 days of the visit as shown in Table 6.1-1. Group A (Arms 2 and 3) and Group B evaluations at week 4 must occur -4/+7 days of the visit, weeks 8 through 32 must occur ±7 days of the visit, and after week 32 must occur ±14 days of the visit as shown in Tables 6.1-2 and 6.1-3.

Missed Vaccination Visits
If any participant misses the week 4 visit (visit window -4/+7 days), reschedule as soon as possible and no later than week 8 (visit window ±7 days). Similarly, if any participant in Group A, Arms 2 and 3, or Group B misses the week 24 visit (visit window ±7 days), reschedule as soon as possible and no later than week 28 (visit window ±7 days). If the participant cannot come in until their next scheduled study visit, combine the two visits.

When the last vaccination in the dose series is delayed as described above, schedule a visit at 8 weeks after the second vaccination for the two-dose

series, or at 4 weeks after the third vaccination for the three-dose series, for HBsAb sample collection to determine SPR. For the three-dose series, this delay may lead to an SPR visit at study week 32. For the two-dose series, there is no corresponding week in the visit schedule that can be applicable when the vaccination delay occurs, and an unscheduled visit is warranted.

For participants who have incomplete vaccine series, participants will be followed on study. Missing dose 2 in a two-dose series results in premature treatment discontinuation; however, if a participant misses the second dose in a three-dose series, this does not lead to premature treatment discontinuation. Dose 3 is allowed to be given if dose 2 is missed.

Remote Data Collection
Study visits may be conducted remotely (e.g., telephone, telehealth) in the following situations:

- **A participant is unable to attend a visit because of illness, lockdown status, or quarantine; the site must inform the CMC (actg.cmca5379@fstrf.org)**
- **The site is temporarily unable to conduct non-essential visits in the clinic; the site must inform the CMC (actg.cmca5379@fstrf.org)**

Remote visits should be conducted during the visit window according to the SOE. Regardless of the situation, sites should document which visits were conducted remotely. For visits that are conducted remotely, the site should attempt to obtain as much of the visit-specific required information based on the SOE as possible and record it on the relevant eCRF.

In addition to the remote visit, the participant should be scheduled for an in-person visit for all evaluations that were not conducted at the remote visit. If the in-person visit evaluations are outside of the visit window, have the participant in as soon as possible for safety-related evaluations as an unscheduled visit. If within a week of the next scheduled visit window, then wait for the next scheduled visit and add any safety lab evaluations not already being performed. If the participant is unable or prefers not to come to the site for a visit, priority safety labs are permitted to be done at a local lab or as part of the standard of care. Record these on an eCRF. The priority safety labs include: chemistry, hematology, and liver function tests.

We ask the sites to prioritize sample collection for HBsAb testing for SPR determination. Primary SPR determination occurs at week 12 for Arm 1 in Group A, and week 28 for Arms 2 and 3 in Group A and for Group B when vaccines are administered as prescribed. If there is a need to limit in-person interactions at the site, the in-person component can be restricted to the blood draw, and the remaining visit evaluations can be completed remotely.

Study Completion Evaluations
Week 72 will be the participant's final scheduled visit on-study.

6.2.4 Discontinuation Evaluations

Evaluations for Randomized or Registered Participants Who Do Not Start Study Treatment
All eCRFs must be keyed for the period up to and including the entry visit. No other evaluations are needed.

Premature Treatment Discontinuation Evaluations
Participants who prematurely permanently discontinue study vaccination series will not have the discontinuation evaluations performed. Participants should continue to attend all study visits and receive study evaluations per section 6.1. They will be followed on study/off study treatment through completion of the study.

Premature Study Discontinuation Evaluations
Participants who prematurely discontinue from the study before week 28 will have the discontinuation evaluations performed per the SOE prior to being taken off the study.

Group A, Arm 1, and Group B participants who prematurely discontinue from the study after week 28 will only have a clinical assessment, pregnancy test, and serum for HBsAb performed prior to being taken off the study.

Group A, Arms 2 or 3 participants who prematurely discontinue from the study after week 28 will only have a clinical assessment, pregnancy test, and serum for HBsAb performed prior to being taken off the study; however, if they discontinue after week 28 but before the week 48 visit, they will also have plasma and PBMC stored for immunologic and latency testing. Plasma and PBMC for immunologic and latency testing will not be stored at the discontinuation visit if the participant discontinues after week 48.

6.3 Instructions for Evaluations

All clinical and laboratory information required by this protocol is to be present in the source documents. Sites must refer to the Source Document Guidelines on the DAIDS website for information about what must be included in the source document: **https://www.niaid.nih.gov/sites/default/files/score-source-documentation-requirements.pdf**.

All stated evaluations are to be recorded on the eCRF unless otherwise specified. Refer to section 7.0 for information on the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table), and AE reporting requirements.

The protocol team and/or study monitoring entity (e.g., DSMB) may determine that additional source data associated with procedures or evaluations performed per

protocol should be entered into eCRFs so that the data can be used for analysis or to otherwise assist with interpretation of study findings. In such cases, sites will be officially instructed to enter the additional data into eCRFs from available source documentation.

6.3.1 Documentation of HIV-1

Section 4.1.1 specifies assay requirements for HIV-1 documentation. HIV-1 documentation is not recorded on the eCRF.

6.3.2 Medical History

The medical history must include all signs and symptoms regardless of grade and all diagnoses identified by the ACTG criteria for clinical events and other diagnoses regardless of grade within the past 30 days. In addition, the following diagnoses should be recorded on the eCRF regardless of when the diagnosis was made:

- AIDS-defining conditions
- Bone fractures (verbal history accepted)
- Coronary artery disease
- Cerebrovascular disease (history of stroke)
- Cancer (exclusive of basal/squamous cell skin cancer)
- Diabetes
- Tuberculosis
- Chronic HCV (active or inactive)
- Chronic kidney disease
- Hypertension
- Hypercholesterolemia

Any allergies to any medications and their formulations must also be documented.

6.3.3 Medication History

A medication history must be present, including start and stop dates. The table below lists the medications that must be included in the history.

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Within 60 days prior to entry
HBV vaccination[1]	Complete history
Immune-based therapy	Within 1 years prior to entry
Blinded study treatment	Within 1 years prior to entry
HIV-1-related vaccines	Within 1 years prior to entry
COVID-19 vaccines	**Complete History**

Medication Category	Complete History or Timeframe
Prescription drugs for treatment of opportunistic infections	Within 60 days prior to entry
Prescription drugs for prophylaxis of opportunistic infections	Within 60 days prior to entry
Prescription drugs (other)	Within 45 days prior to entry
Herbal/dietary supplements	Within 45 days prior to entry
Sex-hormone medications or sex-hormone analogues or antagonists[2]	Within 1 year except as noted below

[1] If available, record dates, dose, and specific vaccine name (e.g., Hepatavax, ENGERIX-B, Twinrix) on the eCRF at screening.
[2] Includes: hormone-releasing IUDs (e.g., Mirena inserted in the last 5 years); oral, injectable, implanted, or patch contraceptives; vaginal ring, creams, or inserts; estrogen, progesterone, or testosterone therapy; leuprolide or other synthetic gonadotropin-releasing hormone; tamoxifen, raloxifene, aromatase inhibitors or any other androgen, estrogen, or progesterone analogue or antagonist therapy.

6.3.4 Clinical Assessments

Complete Physical Examination
A complete physical examination will be performed at screening and is to include at a minimum an examination of the skin, head, mouth, and neck; auscultation of the chest; cardiac examination; abdominal examination; and examination of the lower extremities for edema. The complete physical examination will also include vital signs (temperature, pulse, respiration rate, and blood pressure).

Targeted Physical Examination
Post-screening, per the SOE, a targeted physical examination is to include vital signs (temperature, pulse, and blood pressure), and is to be driven by any previously identified or new signs or symptoms including diagnoses that the participant has experienced since the last visit.

Respiration Rate
Respiration rate is required to be recorded on the eCRF at screening, entry, and week 4 for Group A (Arm 1) and at screening, entry, and weeks 4 and 24 for Group A (Arms 2 and 3) and Group B.

Height
Height is required to be recorded on the eCRF at study entry only.

Weight
Weight is required to be recorded on the eCRF at study entry only.

Tobacco Use
History of smoking tobacco, including the number of cigarettes smoked per day and the number of years the participant smoked, is required to be recorded on the eCRF at study entry only.

Pregnancy
Post-entry, see section 8.2 for collection requirements for pregnancy.

Refer to section 7.2 for AE collection requirements and section 7.3.2 for events that meet EAE reporting requirements.

Concomitant Medications
Post-entry, the following ongoing, new, and discontinued concomitant medications must be recorded on the eCRFs:

- Sex-hormone medications or sex-hormone analogues or antagonists (see section 6.3.3 for examples).
- Corticosteroids
- Intravenous immunoglobulins
- Inactivated or live virus vaccine
- **Vaccines (experimental or standard of care, including COVID-19 vaccines and COVID-19 booster vaccines)**
- Intravenous immunoglobulin therapy
- All immunotherapeutic, immunomodulators, steroids, and other immunosuppressives
- Antiretrovirals
- Any concomitant medication associated with an SAE or medically attended adverse event (MAAE)
- Any concomitant medication associated with a Grade ≥2 AE
- Any concomitant medication associated with **Grade ≥1** local and systemic injection reactions within 7 days after any study vaccine injection.

Study Treatment Modifications
All modifications to study vaccine including initial doses, missed doses, and permanent discontinuation of treatment will be recorded on the eCRFs.

6.3.5 Laboratory Evaluations

At screening and entry all laboratory values must be recorded on the eCRF. For post-entry assessments, record on the eCRF all laboratory values for hemoglobin, creatinine, AST, ALT, and platelet counts regardless of grade; record abnormal laboratory findings as per section 7.2.

Hematology
Hemoglobin, hematocrit, red blood cells (RBC), mean corpuscular volume (MCV), white blood cell count (WBC), differential WBC, absolute neutrophil count (ANC), platelets.

Liver Function Tests
Total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, indirect bilirubin.

INR
To be performed at a local laboratory.

Chemistry
Glucose, creatine kinase, electrolytes (e.g., sodium, potassium, chloride, phosphate, bicarbonate), calcium, creatinine, blood urea nitrogen (BUN), total protein, albumin, globulin (globulin is calculated: total protein minus total albumin).

Hemoglobin A1c
Record HbA1c per the SOE.

Pregnancy Testing
Participants of reproductive potential who can become pregnant: Serum or urine β-HCG (urine test must have a sensitivity of <25 mIU/mL). Pregnancy testing result**s** must be negative **within 2 days** prior to the participant receiving HEPLISAV-B or ENGERIX-B. **Post-entry, n**ote that a subsequent pregnancy test is not required for pregnant participants who consented to continue with the study. Record pregnancy and pregnancy outcome per section 8.2.

6.3.6 Immunologic Studies

CD4+/CD8+
Screening absolute CD4+/CD8+ count and percentages must be performed within 180 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

For entry and post-entry evaluations, all laboratories must possess a CLIA certification or equivalent (US sites) or IQA certification (non-US sites).

HBsAg Qualitative and HBcAb Total
Qualitative HBsAg and HBcAb total will be performed by the site's local laboratory per the SOE for individuals without documented history of HBsAg and HBcAb or with history of HBsAg positive or HBcAb positive results. Results will not be collected on an eCRF.

Serum for HBsAb
Serum HBsAb will be collected, tested, and stored per the SOE. Refer to the A5379 Laboratory Processing Chart (LPC) for detail.

6.3.7 Virologic Studies

The A5379 LPC provides instructions for processing, storing, and shipping the samples described below.

Plasma HIV-1 RNA
Screening HIV-1 RNA must be performed within 180 days prior to study entry at a laboratory that possesses a CLIA certification or equivalent (US sites) or VQA certification (non-US sites). Eligibility will be determined based on the screening value.

For entry (Group A, Arms 2 and 3 only) and post-entry (both Groups), HIV-1 RNA testing must be performed at the protocol-designated laboratory.

6.3.8 Stored Plasma and PBMC

Only sites certified by the IQA Cryopreservation PT Program at the Duke Human Vaccine Institute are required to collect PBMCs.

Stored Plasma and PBMC for Immunologic and Latency Testing
For Group A, Arms 2 and 3 only, plasma and PBMC will be stored for immunologic and latency studies per the SOE.

Analyses on Stored Specimens
For Group A, Arms 2 and 3 only, PBMC will be stored for genetic testing per the SOE.

Plasma for cytokines and chemokines will be measured with the assay per the manufacturer's recommendations.

RNA-Seq
Participants will undergo isolation of specific cell types and the cell subsets will be analyzed via RNA-Seq.

Analysis of HBV- and HIV-specific T Cell Responses
Samples for assessment of T cell responses will be collected at the indicated time points. Depending on availability of PBMCs, assays will be performed on selected samples to further characterize cross-reactivity, function, and phenotype of the induced response.

Analysis of the HIV Reservoir
CD4+ T-cells will be isolated from PBMC at time points indicated in the SOE. The following will be measured at baseline and at week 28 after first injection with HEPLISAV-B (Group A, Arms 2 and 3): 1) HIV reservoir size; 2) cell associated HIV-1 RNA; and 3) total DNA levels.

6.3.9 Vaccine Administration (HEPLISAV-B and ENGERIX-B)

All study products should be administered according to section 5.0 and the SOE.

Participants will be counseled on the importance of receiving all vaccine doses given the probability of a suboptimal response for participants that do not receive all doses.

Vaccine should be deferred for fever on the day of vaccination defined as oral temperature >38°C, until the participant is afebrile for 24 hours. If participant remains febrile and cannot be rescheduled within the visit window, reschedule according to section 6.2.3. It is acceptable to defer the injection for either time point. Refer to section 6.2.3 about missed vaccination visits.

6.3.10 Post-vaccination Assessment

Participants should remain in clinic for 30 minutes after injection. Record oral temperature 30 minutes after injection in source documents. At the end of this observation period, assess for any post-injection reactions (PIRs) and AEs, and record any reportable events on the eCRF, as described in section 7.0.

6.3.11 Diary Card

A diary card along with a standard measuring device and thermometer will be distributed to each participant per the SOE. The diary card collects temperature and reactions to the vaccine (i.e., pain, redness, and swelling at or near the injection site, malaise, headache, myalgia, and fatigue) that the participant records for 7 days post vaccine administration.

The completed diary card will be collected at the next study visit following the vaccine administration. Entries will be reviewed. AEs identified will be recorded on the eCRF according to section 7.2. Any information that meets the study eCRF data entry requirements should be entered on the associated eCRF(s).

The diary card is posted on the PSWP.

6.3.12 Remote Contact

Participants will be contacted via e-mail, text message, or telephone by study staff 3-5 business days after vaccination study visits **(at weeks 0, 4, and 24 for Group A, Arm 2 and 3, and Group B and at weeks 0 and 4 for Group A, Arm 1)** to remind them to complete the diary card (i.e., document any injection site reactions). Three to five business days prior to study visits at weeks 4, 8, and 28 (contact for the week 28 study visit is not applicable for Group A, Arm 1), participants will be contacted via e-mail, text message, or telephone by study staff to remind them to bring the diary card at the next study visit. Contact will be recorded in the source documents and will not be recorded on the eCRF. Refer to the Manual of Procedures (MOPS) for remote contact guidance.

7.0 ADVERSE EVENTS AND STUDY MONITORING

7.1 Definition of Adverse Events

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or diagnosis that occurs in a study participant during the conduct of the study REGARDLESS of the attribution (i.e., relationship of event to medical treatment/study product/device or procedure/intervention). This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition.

7.2 Adverse Event Collection Requirements for This Protocol

All AEs must be recorded on the eCRFs if any of the following criteria have been met.

- All Grade ≥2 AEs.
- All AEs that led to a change in study treatment regardless of grade.
- All AEs meeting SAE definition or EAE reporting requirement.
- All **Grade ≥1** local and systemic injection reactions within 7 days of any study vaccine injection.
- All MAAEs, defined as AEs with medically attended visits that were not routine visits for physical examination or vaccination, such as visits for hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from a medical personnel for any reason.
- All potential immune-mediated AEs regardless of grade. A list of potential immune-mediated AEs is posted on the A5379 PSWP.

Sites will assess AE relationship to investigational product based on the stated criteria written in the DAIDS EAE Manual Version 2.0 for all AEs, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

NOTE: SAEs or events meeting EAE reporting requirements should also be entered into the DAIDS Adverse Experience Reporting System (DAERS), an Internet-based reporting system.

All AEs that are reported must have their severity graded. To grade AEs, sites must refer to the DAIDS AE Grading Table corrected Version 2.1, July 2017, which can be found on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

Targeted Local and Systemic Adverse Reactions

Participants will self-monitor for local and systemic adverse reactions using diary cards for a 7-day period starting on the day of vaccination. The completed diaries will be used by site staff to record any AEs.

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above).

7.3 Expedited Adverse Event (EAE) Reporting to DAIDS

7.3.1 Expedited Reporting of Adverse Events to DAIDS

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

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

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

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

7.3.2 Reporting Requirements for this Study

- The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study.
- The study agents for which expedited reporting are required are:
  - Hepatitis B Vaccine (Recombinant) Adjuvanted (HEPLISAV-B)
  - Hepatitis B Vaccine (Recombinant) (ENGERIX-B)
- In addition to the EAE Reporting Category identified above, other AEs that must be reported in an expedited manner are*:*
  - All myocardial infarctions
  - Strokes
  - New onset of diabetes
  - Herpes zoster
  - Autoimmune diseases
  - Any potential immune-mediated AEs
  - Thromboembolic diseases
  - Deep venous thrombosis (DVT)

- Pulmonary embolism (PE)
- Any abnormal pregnancy outcomes

7.3.3 Grading Severity of Events

The DAIDS AE Grading Table corrected Version 2.1, July 2017, must be used and is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

7.3.4 Expedited AE Reporting Period

- The expedited AE reporting period for this study is the study duration (i.e., through week 72).
- After the protocol-defined AE reporting period, unless otherwise noted, only suspected, *unexpected* serious adverse reactions (SUSARs), as defined in Version 2.0 of the EAE Manual, will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).

7.4 Study Monitoring

The protocol core team (which includes the chairs and medical officer) will monitor the conduct and safety of the study via regular summaries of accrual, study discontinuation, data completeness, and AEs, as appropriate.

The DAIDS clinical representative will review and assess select EAE reports for potential impact on the study participant safety and protocol conduct as per DAIDS policies, guidance documents, and SOPs as applicable. Additionally, the DAIDS clinical representative will review aggregated AE summaries pooled across treatment arms prepared by the SDAC following the schedule for Data and Safety Monitoring Board (DSMB)-monitored studies.

The study will undergo interim review at least annually by a NIAID-appointed DSMB. The first interim review will occur no more than 1 year after the enrollment of the first study participant. An interim review may also be convened if a concern is identified by the DAIDS clinical representative, the study chairs, or study statistician in consultation with the team. See sections 10.1 and 10.5 for statistical and other considerations related to interim monitoring.

Detailed plans for study monitoring will be outlined in a Study, Progress, Data and Safety Monitoring Plan developed by the Statistical and Data Management Center (SDMC) before clinical trial initiation. See section 10.5 for further information on the Data and Safety Monitoring.

8.0 CLINICAL MANAGEMENT ISSUES

8.1 Toxicity

All vaccines in this study are expected to be well tolerated. Injection-site reactions are expected to spontaneously subside. Local pruritus and pain can be treated with oral medications. If significant symptoms of pain and induration persist for more than 12 hours, an ice pack may be applied locally for 30 minutes every 2 hours, as needed. Use of an ice pack within 12 hours post-vaccination and after the onset of symptoms is discouraged as it may interfere with the action of the vaccine.

Results related to participant safety and significant clinical findings requiring medical attention and follow up will be provided to the participant and their treating medical provider.

Vaccine-related Hypersensitivity
A participant who develops study vaccine-related hypersensitivity reactions believed to be secondary to any of the constituents of HEPLISAV-B or ENGERIX-B will not receive any further dosing of study vaccines. These reactions may manifest with signs and symptoms that may include, but are not limited to fever, chills, headache, rash, pruritus, hypo- or hypertension, bronchospasm, or other symptoms. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Participants should be carefully observed until the complete resolution of all signs and symptoms. In each case of vaccine related hypersensitivity, the site investigator should institute treatment measures according to the best available medical practice. The CMC must be notified within 24 hours by e-mail at actg.cmcA5379@fstrf.org.

8.2 Pregnancy

Pregnancy and pregnancy outcome will be recorded on the eCRFs. The CMC (actg.cmca5379@fstrf.org) must be notified of all on study pregnancies.

US sites must inform participants of the voluntary HEPLISAV-B pregnancy registry if a pregnancy occurs within 90 days **after** HEPLISAV-B administration and provide the registry telephone number: 1-844-443-7732. US sites should encourage the participant to call; however, the registry is voluntary and the participant may choose to enroll or not. The HEPLISAV-B pregnancy registry is restricted to US sites only.

Pregnancies that occur on study should also be reported prospectively to The Antiretroviral Pregnancy Registry. More information is available at www.apregistry.com. Telephone: 800-258-4263; Fax: 800-800-1052. (For studies conducted at sites outside the United States, report to The Antiretroviral Pregnancy Registry—Telephone: 910-679-1598; Fax: 44-1628-789-666 or 910-256-0637.)

Pregnancy Outcomes and Reporting
Because the study vaccines hold the prospect of direct benefit for the pregnant participant, participants who have received any dose of study vaccine and become

pregnant on study will be offered the option to stay on study with study vaccine or stop study vaccine. Individuals on HEPLISAV-B who choose to stay on the study vaccine will be counseled on the lack of adequate safety, efficacy, and fetal toxicity data of the vaccine in pregnant individuals. All pregnant participants will need to complete a pregnancy-specific consent process. Study follow up will continue according to section 6.0 for the duration of the study. In case of termination of pregnancy, the participant will continue with the evaluations and vaccination schedule per the SOE. The investigator and study team will have no part in any decision related to terminating the pregnancy.

If a participant has completed the study or chooses to discontinue from the study before the end of the pregnancy, then site staff should request permission to contact her regarding pregnancy outcomes at the end of pregnancy. If the information is obtained, pregnancy outcomes will be submitted on an eCRF at the end of the pregnancy.

8.3 Breastfeeding

There are no data to inform on the excretion of HEPLISAV-B in human breast milk. It is not known what impact HEPLISAV-B could have on the breastfed infant or on milk production and excretion by the mother.

9.0 CRITERIA FOR DISCONTINUATION

9.1 Permanent and Premature Treatment Discontinuation

- Vaccine-related toxicity/hypersensitivity reaction or other severe reaction to the study vaccine (see section 8.1 Toxicity).
- An SAE that is assessed as related to study vaccination.
- A new onset or worsened potentially immune-mediated AE, regardless of assessment of relationship to study vaccination.
- Requirement for prohibited concomitant medications (see section 5.5).
- Request by participant to terminate treatment.
- Clinical reasons believed life-threatening by the physician, even if not addressed in the toxicity section of the protocol.
- **Missed 2nd dose in the allowed timeframe (see section 6.2.3) for a two-dose series.**
- **Missed 3rd dose in the allowed timeframe (see section 6.2.3) for a three-dose series.**

9.2 Premature Study Discontinuation

- Request by the participant to withdraw.
- Failure to start study treatment.
- At the discretion of the IRB/EC, FDA, NIAID, Office for Human Research Protections (OHRP), other government agencies as part of their duties, investigator, or industry supporter.

10.0 STATISTICAL CONSIDERATIONS

10.1 General Design Issues

A5379 is a prospective, open-label study to evaluate immunogenicity of the HBV vaccine HEPLISAV-B in two study populations living with HIV: prior HBV vaccine recipients who are deemed non-responders (Group A) and individuals who are naïve to HBV vaccination (Group B). The study is designed separately for the two study populations and will be conducted as separate evaluations for all primary and key secondary analyses. Because the study populations for Groups A and B are different, no adjustment of type I error is planned for conducting two population studies under the same protocol mainly for administrative efficiency.

For the study arms with three-dose vaccine administrations (at weeks 0, 4, and 24), seroprotection response (SPR, HBsAb ≥10 mIU/mL) at 4 weeks after the vaccination series (at week 28) will be assessed for the primary analysis. For the HEPLISAV-B arm with a two-dose vaccine administration (at weeks 0 and 4), SPR at 8 weeks after the vaccination series (at week 12) will be assessed for the primary analysis. Section 2.2 provides the rationale behind the choice of outcome measure for the primary analysis.

10.1.1 Group A (Non-responders)

The study in Group A is designed to address two primary objectives:

1. To determine if the HEPLISAV-B vaccine administered as a two-dose vaccination series at weeks 0 and 4 (Arm 1) is non-inferior to the standard ENGERIX-B vaccine administered as a three-dose vaccination series at weeks 0, 4, and 24 (Arm 3).

2. To determine if the HEPLISAV-B vaccine administered as a three-dose vaccination series at weeks 0, 4, and 24 (Arm 2) is superior to the standard ENGERIX-B vaccine administered as a three-dose vaccination series at weeks 0, 4, and 24 (Arm 3).

The study is designed as an open-label three-arm study, where participants are randomized to the following study arms:

Arm 1: Two doses of HEPLISAV-B at weeks 0 and 4
Arm 2: Three doses of HEPLISAV-B at weeks 0, 4, and 24
Arm 3: Three doses of ENGERIX-B at weeks 0, 4, and 24

Arm 3 serves as the control arm for both comparisons in Group A. The first primary objective in Group A will be addressed by comparing Arm 1 to Arm 3, and the second primary objective in Group A will be addressed by comparing Arm 2 to Arm 3. Arm 1 allows the assessment of long-term antibody responses at 48 weeks after the two-dose vaccination series. It is necessary to support the primary findings on SPR with positive findings on the long-term antibody

responses 48 weeks later. The latter antibody response is proposed as a key secondary outcome, to be evaluated as an important supporting analysis.

In Group A, a two-sided type I error rate is targeted at the pre-specified overall alpha level of 5% for the two primary analysis comparisons. To preserve the overall type I error rate in Group A and to allow flexible interim monitoring, a Bonferroni correction is applied, and a two-sided type I error rate of 2.5% each for the comparison between Arm 1 and Arm 3 and for the comparison between Arm 2 and Arm 3 is allocated. Interim monitoring is considered independently for the two primary objectives as follows.

1. For the primary objective on the comparison between Arm 1 and Arm 3, interim monitoring will not include early formal non-inferiority analyses using the accumulating data on the primary outcome for early study conclusion on non-inferiority. This is because the long-term antibody data in the study provide important supporting information on how the primary results in these study arms should be interpreted for future guidance. As such, the sample size for Arm 1 is not adjusted for interim looks. Interim monitoring on SPR will focus on assessments related to potential harm, where Arm 1 may be closed early if there is sufficiently compelling evidence in the interim data that suggest poor response to the two-dose vaccination series that may be deemed harmful.

2. For the primary objective on the comparison between Arm 2 and Arm 3, interim monitoring will include efficacy analyses, if the enrollment rate allows such early looks to be meaningful in assessing future conduct of the study. The sample sizes for Arms 2 and 3 are adjusted for the potential interim efficacy looks. Interim monitoring considerations will also include assessment for compelling evidence of lack of benefit and possibly potential harm in continuing Arm 2. Interim looks strictly based on “futility" which (in statistical usage) are based on the potential failure to reject the specified null hypothesis are not planned in this study. (See Freidlin et al. [**19**] regarding interim looks related to futility versus inefficacy.)

   The sample size of 187 in each arm was determined by the larger of the sample sizes needed for the two primary analysis comparisons. The sample size of 187 each in Arms 1 and 3 was determined to show non-inferiority of two-dose administration of HEPLISAV-B (Arm 1) compared to the standard three-dose ENGERIX-B vaccination (Arm 3, control). The team anticipates that two doses of HEPLISAV-B (Arm 1) will result in a higher SPR proportion than the control arm (Arm 3), but the objective is to show non-inferiority with a margin of 10%. That is, the study seeks to show that the amount by which the two-dose HEPLISAV-B series (Arm 1) is inferior to the control (Arm 3) is less than a 10% difference in the SPR proportions. Therefore, the study is powered for a non-inferiority design but under the assumption that the SPR proportion is somewhat higher with two-dose administration of HEPLISAV-B. The non-inferiority margin of 10% was chosen in accordance with a previous FDA study on HEPLISAV-B. (See section 2.2, Rationale.) And the sample

size of 187 in Arm 2 provides good power to show superiority of three-dose administration of HEPLISAV-B (Arm 2) compared to the standard three-dose ENGERIX-B vaccination (Arm 3, control).

These sample sizes provide at least 80% power to conclude in two statistical tests that 1) Arm 1 is non-inferior to Arm 3, and 2) Arm 2 is superior to Arm 3, each with a well-controlled two-sided type I error of 2.5% with Bonferroni correction for the two primary objectives. The assumption of 70% SPR proportion at 4 weeks after the vaccination series for the control arm (Arm 3) is based on the literature review of a limited number of studies on repeat vaccination in those who failed a primary vaccination series (See section 2.1, Background.) The assumption of 75% SPR proportion in HEPLISAV-B Arm 1 and 85% SPR proportion in Arm 2 are based on the results of prior HEPLISAV-B studies. (See section 2.1.)

10.1.2 Group B (HBV Vaccine-naïve)

Group B consists of individuals who have no known prior history of HBV vaccination. The study in Group B will be conducted as a prospective, single-arm study of the three-dose vaccination series with HEPLISAV-B in HBV vaccine-naïve participants. The primary study objective is to evaluate seroprotective response (SPR) at 4 weeks after the vaccination series.

Group B study is designed to conclude that the true SPR proportion is greater than 55% with good precision. This will be assessed by examining if a two-sided 95% confidence interval (CI) for the sample proportion is entirely above 55%. This is equivalent to showing that the SPR proportion is higher than 55% in a one-sided test with a type I error of 2.5%, where the aim is to rule out SPR proportions below or equal to 55%. The threshold of 55% was chosen based on the completed A5220 study. (See section 2.2.)

Group B sample size of 73 participants was chosen to show with 90% power that the SPR proportion is greater than 55% in this study population and to account for a potential missed visit or loss to follow-up prior to the primary outcome visit at week 28. Assuming the underlying SPR proportion is 75% with a three-dose vaccine series with HEPLISAV-B and assuming no more than 10% loss to follow-up prior to week 28, this sample size would provide the targeted analysis sample size of 65. The team considers an SPR proportion of 75% to be plausible based on the results of HEPLISAV-B studies in individuals with diabetes and in individuals with kidney disease, which are deemed to be populations challenged with low vaccine responses (refer to section 2.1) The targeted sample size will provide good precision around the estimated SPR proportion to give guidance on the use of HEPLISAV-B vaccine in HIV-1 positive persons without prior HBV vaccination.

No formal interim efficacy analysis is planned because the aim of Group B is to provide an SPR estimate with good precision for persons living with HIV. Interim monitoring will consist of data reviews to ensure that there is no harm and the study is conducted appropriately.

10.1.3 Groups A and B

In both Groups A and B, the primary outcome of achieving SPR after the vaccination series (at week 28 with a three-dose series and at week 12 with a two-dose series) may be evaluated prior to the completion of study follow-up at week 72. The primary analysis timeline will be driven by the last participant's completion of the primary outcome visit, rather than the study completion date. As such, the primary analysis timelines will be derived separately for Groups A and B. Results from the **SPR** analysis may be presented publicly, for example at a conference, upon completion of relevant data prior to the study database finalization.

The final analysis for the two study groups **may occur separately after complete follow-up and data finalization.**

The primary analysis on SPR will be conducted on all study-eligible participants who receive at least one vaccine. Each data analysis will be conducted on participants with available data, under the assumption of missing at random. (See Li et al. [**20**] on handling missing data in vaccine clinical trials.)

10.2 Outcome Measures

Primary and secondary outcome measures listed below will be addressed in the primary Statistical Analysis Plan (SAP), which will define the content of the Primary Analysis Report. This report will form the basis for the primary study manuscript and results reporting to **https://**ClinicalTrials.gov. Outcomes of interest for secondary and exploratory objectives intended for subsequent publications are to be listed under "Other Outcome Measures."

10.2.1 Primary Outcome Measures

For Group A Primary Analyses:

10.2.1.1 [Objectives 1.2.1 and 1.2.2] Seroprotection response defined as HBsAb ≥10 mIU/mL at 8 weeks after the two-dose series (week 12) in Arm 1 and at 4 weeks after the three-dose series (week 28) in Arms 2 and 3.

10.2.1.2 [Objective 1.2.4] Reported AEs from study vaccination initiation to study discontinuation.

For Group B Primary Analyses:

10.2.1.3 [Objective 1.2.3] Seroprotection response defined as HBsAb ≥10 mIU/mL at 4 weeks after the vaccination series (week 28).

10.2.1.4 [Objective 1.2.4] Reported AEs from study vaccination initiation to study discontinuation.

10.2.2 Secondary Outcome Measures

For Group A Secondary Analyses:

10.2.2.1 HBsAb titer at the following study visits in Arm 1:
- Week 4 [Objective 1.3.6]
- Week 8 [Objectives 1.3.3, 1.3.5, and 1.3.6]
- Week 12 [Objectives 1.3.1, 1.3.3, 1.3.5, and 1.3.6]
- Week 24 [Objective 1.3.6]
- Week 28 [Objectives 1.3.3 and 1.3.5]
- Week 52 [Objectives 1.3.3 and 1.3.5]
- Week 72 [Objective 1.3.12]

10.2.2.2 Seroprotection response defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 1:
- Week 4 [Objective 1.3.6]
- Week 8 [Objectives 1.3.3, 1.3.5, and 1.3.6]
- Week 12 [Objectives 1.3.3, 1.3.5, and 1.3.6]
- Week 24 [Objective 1.3.6]
- Week 28 [Objectives 1.3.3 and 1.3.5]
- Week 52 [Objectives 1.3.3 and 1.3.5]
- Week 72 [Objective 1.3.12]

10.2.2.3 HBsAb titer at the following study visits in Arm 2:
- Week 4 [Objective 1.3.6]
- Week 8 [Objective 1.3.6]
- Week 12 [Objective 1.3.6]
- Week 24 [Objective 1.3.6]
- Week 28 [Objectives 1.3.2 and 1.3.5]
- Week 32 [Objectives 1.3.4 and 1.3.5]
- Week 48 [Objectives 1.3.4 and 1.3.5]
- Week 72 [Objectives 1.3.4, 1.3.5, and 1.3.12]

10.2.2.4 Seroprotection response defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 2:
- Week 4 [Objective 1.3.6]
- Week 8 [Objective 1.3.6]
- Week 12 [Objective 1.3.6]

- Week 24 [Objective 1.3.6]
- Week 28 [Objective 1.3.5]
- Week 32 [Objectives 1.3.4 and 1.3.5]
- Week 48 [Objectives 1.3.4 and 1.3.5]
- Week 72 [Objectives 1.3.4, 1.3.5, and 1.3.12]

10.2.2.5 HBsAb titer at the following study visits in Arm 3:

- Week 4 [Objective 1.3.6]
- Week 8 [Objective 1.3.6]
- Week 12 [Objective 1.3.6]
- Week 24 [Objective 1.3.6]
- Week 28 [Objectives 1.3.1, 1.3.2, and 1.3.3]
- Week 32 [Objectives 1.3.3 and 1.3.4]
- Week 48 [Objectives 1.3.3 and 1.3.4]
- Week 72 [Objectives 1.3.3 and 1.3.4]

10.2.2.6 Seroprotection response defined as HBsAb ≥10 mIU/mL at the following study visits in Arm 3:

- Week 4 [Objective 1.3.6]
- Week 8 [Objective 1.3.6]
- Week 12 [Objective 1.3.6]
- Week 24 [Objective 1.3.6]
- Week 28 [Objective 1.3.3]
- Week 32 [Objectives 1.3.3 and 1.3.4]
- Week 48 [Objectives 1.3.3 and 1.3.4]
- Week 72 [Objectives 1.3.3 and 1.3.4]

10.2.2.7 Grade ≥2 AEs within 4 weeks after each injection [Objective 1.3.10]

For Group B Secondary Analyses:

10.2.2.8 HBsAb titer at the following study visits:

- Weeks 4, 8, 12, and 24 [Objective 1.3.9]
- Week 28 [Objective 1.3.7]
- Weeks 32, 48, and 72 [Objective 1.3.8]

10.2.2.9 Seroprotection response defined as HBsAb ≥10 mIU/mL at the following study visits:

- Weeks 4, 8, 12, and 24 [Objective 1.3.9]
- Weeks 32, 48, and 72 [Objective 1.3.8]

10.2.2.10 Grade ≥2 AEs within 4 weeks after each injection [Objective 1.3.10]

For Exploratory Analyses Combining Groups A and B:

10.2.2.11 HBsAb titer at the following study visits in Group A, Arm 2, and Group B [Objective 1.4.1]: Weeks 4, 8, 12, 24, 28, 32, 48, and 72

10.2.2.12 Seroprotection response defined as HBsAb ≥10 mIU/mL at the following study visits in Group A, Arm 2, and Group B [Objective 1.4.1]: Weeks 4, 8, 12, 24, 28, 32, 48, and 72

10.2.3 Other Outcome Measures

10.2.3.1 HBV surface antigen-specific B and T-cell responses

10.2.3.2 Innate immune soluble factors

10.2.3.3 Genes and adaptive cell phenotypes (to be identified when the assay is determined)

10.2.3.4 Cell-associated HIV-1 RNA in CD4+ T-cells

10.2.3.5 Frequency of latently infected cells

10.2.3.6 Total DNA levels

10.2.3.7 HIV-1 specific immune responses, T-cell activation, expression of exhaustion markers on T-cells and other levels of HIV-specific immunity and activation (biomarkers to be defined when the assays are identified).

10.3 Randomization and Stratification

At study entry, Group A participants will be randomized in 1:1:1 ratio to Arms 1, 2, and 3. Randomization will use permuted blocks and balancing by main site. Group A will be stratified by sex assigned at birth (male versus female) and diabetes diagnosis status (yes versus no).

All Group B participants will be assigned to receive three doses of HEPLISAV-B.

10.4 Sample Size and Accrual

10.4.1 Group A (Non-responder, N=561)

Group A consists of individuals who have prior history of HBV vaccination but are considered non-responders. There are two primary objectives, and the Group A overall type I error rate of 5% is preserved by applying the Bonferroni correction to allocate a type I error rate of 2.5% to each primary analysis.

Accrual of about 45 participants per month on the average is anticipated. Complete enrollment in about 12.5 months in Group A is anticipated.

10.4.1.1 Non-inferiority Design (Arm 1 and Arm 3 Comparison)

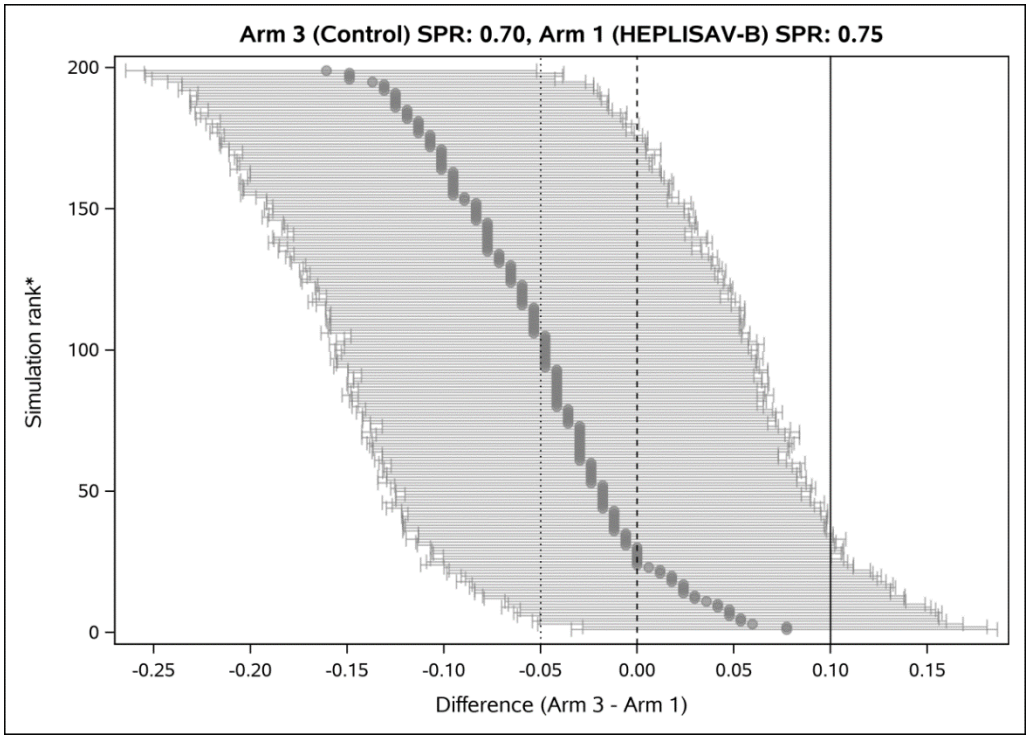
For the primary objective to show that SPR proportion in Arm 1 is non-inferior to the SPR proportion in Arm 3 within the non-inferiority margin of 10%, we assume that 70% in the control arm (Arm 3) will achieve SPR. We assume the proportion of participants achieving SPR with two doses of HEPLISAV-B (Arm 1) will be higher at 75%. As a non-inferiority design, this comparison is powered to show that the SPR proportion in Arm 1 is not lower than that of Arm 3 (control) by more than the pre-specified non-inferiority margin of 10%. A sample size of 168 each in Arm 1 and Arm 3 achieves 80% power to detect a difference between the two proportions of less than 10%, in a one-sided test with type I error of 1.25% using normal approximation. Assuming no more than about 10% missing data for SPR, which includes loss to follow-up within each study arm prior to the primary outcome visit, the study sample size is increased to 187 per study arm. Table 10.4.1.1-1 below shows sample sizes for various scenarios for the Arm 1 and Arm 3 non-inferiority comparison with a non-inferiority margin of 10%. Arm 1 is anticipated to have better SPR proportion than Arm 3 (control), and scenarios where Arm 1 has worse response are not considered here.

Table 10.4.1.1-1: Group A (non-responder) Non-inferiority Comparison between Arms 1 and 3 with One-sided 1.25% (corresponds to two-sided type I error of 2.5%) after Bonferroni Correction

ENGERIX-B Seroprotection Response (Arm 3, Control)	HEPLISAV-B Seroprotection Response (Arm 1)	Difference (Arm 3 minus Arm 1)	Targeted Sample Size per Arm	Planned Sample Size per Arm (10% loss-inflated)
0.65	0.65 0.70 0.75	0 -0.05 -0.10	N=433 N=185 N=99	N=482 N=206 N=110
0.70	0.70 0.75 0.80	0 -0.05 -0.10	N=400 N=168 N=88	N=445 N=187 N=98
0.75	0.75 0.80 0.85	0 -0.05 -0.10	N=357 N=147 N=75	N=397 N=164 N=84

Figure 10.4.1.1-1 shows possible results of the non-inferiority comparison under the design assumptions of 70% SPR in Arm 3 and 75% SPR in Arm 1. The figure presents the SPR differences (SPR proportion in Arm 3 minus SPR proportion in Arm 1) as point estimates (in solid circles) with two-sided 97.5% confidence intervals with a sample size of 168 each in Arm 1 and Arm 3. For the purpose

of illustrating potential outcomes in this non-inferiority design, potential multiple interim looks and stratification factors are not incorporated in the confidence interval estimation. The confidence intervals that lie entirely below the margin of 10% will be deemed non-inferior. Figure 10.4.1.1-1 shows that about 80% of the confidence intervals lie below the margin of 10%.



**Simulation trials were ranked by the estimate of the SPR difference between Arms 1 and 3. The vertical line at -0.05 represents the assumed SPR difference (Arm 3 - Arm 1), the vertical line at 0 represents no difference in SPR between Arm 3 and Arm 1, and the vertical line at 0.10 represents the 10% non-inferiority margin.*

Figure 10.4.1.1-1: Simulated Point Estimates and 97.5% Confidence Intervals for the Arm 1 SPR Difference from Arm 3 under the Design Assumptions

No formal interim efficacy analysis to conclude non-inferiority of Arm 1 compared to Arm 3 (control) is planned for the first primary objective, and sample size adjustment for interim efficacy monitoring is not made. Guidelines on interim monitoring for Arm 1 are described below in section 10.5. The proposed sample size for Arm 1 and Arm 3 is 187 for each.

10.4.1.2 Superiority Design (Arm 2 and Arm 3 Comparison)

For the primary objective to compare SPR proportion at 4 weeks after the vaccination series between Arm 2 and Arm 3 (control), an increase of 15% is assumed in the proportion of participants achieving

SPR with three doses of HEPLISAV-B (Arm 2). With the sample sizes of 147 participants in each study arm, there is 80% power to detect a difference as significant in a two-sided test at a significance level of 2.5% using normal approximation. Table 10.4.1.2-1 shows sample sizes for various scenarios for the Arm 2 and Arm 3 comparison.

Table 10.4.1.2-1: Group A (non-responder) Comparison between Arms 2 and 3 with Two-sided Type I Error of 2.5% after Bonferroni Correction

ENGERIX-B Seroprotection Response (Arm 3)	HEPLISAV-B Seroprotection Response (Arm 2)	Difference (Arm 2 minus Arm 3)	Targeted Sample Size per Arm
0.65	0.80 0.85	0.15 0.20	N=168 N=88
0.70	0.85 0.90	0.15 0.20	N=147 N=75
0.75	0.85 0.90 0.95	0.10 0.15 0.20	N=303 N=121 N=60

Formal interim efficacy analyses are planned for the Arm 2 and Arm 3 comparison, should the study enrollment allow such interim analyses to be useful to affect the conduct of the study. Assuming no more than three interim analyses for the study and applying the O'Brien and Fleming approach to preserve the two-sided type I error rate at 2.5%, Arm 2 and Arm 3 sample sizes should be at least 149 per study arm. Assuming no more than about 10% loss in the SPR data within each study arm, the targeted study sample size is 166 each for Arm 2 and Arm 3 to retain 80% power. To maintain 1:1:1 randomization across Arms 1, 2, and 3 throughout enrollment, the sample size in Arm 2 is increased to 187. Therefore, the power for the comparison between Arm 2 and Arm 3 is higher than 80%.

10.4.2 Group B (Naïve to HBV vaccination, N=73)

Group B consists of individuals who have no known prior history of HBV vaccination. The study is powered to conclude that the proportion achieving SPR is greater than 55%. Assuming a response proportion of 75%, a sample size of 65 would provide at least 90% power in a two-sided test using normal approximation at a targeted significance level of 5%. Assuming at most 10% missing data, including loss to follow-up prior to the primary outcome visit, the study sample size is increased to 73. Table 10.4.2-1 below shows sample sizes for various responses, where the null rate for response is 55%.

Table 10.4.2-1: Group B (Naïve to HBV Vaccination)

HEPLISAV-B	Difference	Targeted Sample Size	Total Sample Size

Seroprotection	from Null		(Includes 10% LFU)
0.70	0.15	N=113	N=126
0.75	0.20	N=65	N=73
0.80	0.25	N=44	N=49

The table below shows two-sided 95% confidence intervals for the various potential sample SPR proportions, using the Wilson method and the targeted analysis sample size of 65.

Table 10.4.2-2: Group B Confidence Intervals

Sample SPR proportion	95% CI
67.7% (44/65)	(55.6%, 77.8%)
70.8% (46/65)	(58.8%, 80.4%)
73.8% (48/65)	(62.0%, 83.0%)
76.9% (50/65)	(65.4%, 85.5%)
80.0% (52/65)	(68.7%, 87.9%)

Accrual of about six participants per month on the average is anticipated. Complete enrollment in about 12 months in Group B is anticipated.

10.5 Data and Safety Monitoring

10.5.1 Interim Monitoring Guidelines

The study will be monitored by the core protocol team and the independent DAIDS-appointed DSMB. The initial interim data review by the DSMB will occur no later than one year after the enrollment of the first participant in the study in either Group A or B.

10.5.1.1 Group A

(1) Primary Outcome Analysis Comparison Between Arms 1 and 3

Regarding the first primary objective in Group A, early interim efficacy analysis to conclude non-inferiority of Arm 1 compared to the control, Arm 3, will not occur. Long-term antibody results are also needed to guide the recommendation of the two-dose HEPLISAV-B vaccine series.

Early stopping due to concerns on poor vaccine responses in Arm 1 that may be deemed harmful may occur. For this purpose, the SPR estimates for the primary outcome measure will be provided with a two-sided 99.9% confidence interval around the difference in the proportion estimates (Arm 3 minus Arm 1). As a guideline, a lower bound of this confidence interval above 10% may be considered evidence towards poor response in Arm 1 that

suggests potential harm.

The DSMB will review the interim data and make recommendations. If the decision is made that Arm 1 should close early, the sample size of its comparator, Arm 3, may be adjusted as determined by the need for the second primary objective (comparison between Arm 2 and Arm 3).

(2) Primary Outcome Analysis Comparison Between Arms 2 and 3

Formal efficacy interim analyses are planned for the second primary objective on the comparison between Arm 2 and Arm 3 (control arm), should the study enrollment allow such interim analyses to be useful to affect the conduct of the study. The initial interim efficacy analysis on the primary outcome for this comparison is aimed at when at least 40% of the SPR results at 4 weeks after the vaccination series are available for analysis. The Lan-DeMets spending function for type I error (alpha) with O'Brien-Fleming type boundaries will be employed. With this approach, two-sided type I error rate for efficacy at the 0.025 level will be preserved regardless of the number and timing of the analysis. If the confidence interval at the interim look lies entirely above zero and the interim data review identifies no concerns, early stopping of Arm 2 to conclude Arm 2 superiority may occur.

Early stopping due to concerns about poor vaccine responses in Arm 2 may also occur. For this purpose, the SPR estimates for the primary outcome measure will be provided with a two-sided 99.9% confidence interval around the difference in the proportion estimates (Arm 3 minus Arm 2), similar to the assessment of potential harm in Arm 1 discussed above. As a guideline, a lower bound of this confidence interval above 10% may be considered as evidence towards poor response in Arm 2 to suggest potential harm.

The DSMB will review the interim data and make recommendations. The DSMB will weigh the benefits of closing early against the benefits of continuing the study to accumulate additional safety data in this study population. If the decision is made that Arm 2 should close early, the sample size of its comparator, Arm 3, may be adjusted as determined by the need for the first primary objective (comparison between Arm 1 and Arm 3).

10.5.1.2 Group B

An interim efficacy analysis to conclude early that the estimated

single-arm SPR proportion at 4 weeks after the vaccination series exceeds the null proportion (55%) will not be conducted. Establishing a good precision around the SPR estimate and collecting safety information on a reasonable number of study participants living with HIV without prior HBV vaccination are important in Group B.

Early stopping due to concerns about poor vaccine responses may occur. If the study enrollment allows interim analysis on the SPR proportion to be useful to affect the conduct of the study, a two-sided 99.9% confidence interval may be provided with the proportion estimate, and the interval upperbound below 45% (10% lower than the null proportion) may be used as guidance.

10.5.2 Analysis Plan

For the interim analyses, Newcombe confidence intervals on SPR differences from control (Arm 3) will be provided for comparisons in Group A. For the SPR comparisons with Arm 3 in the assessment of potential harm in continuing Arm 1 or Arm 2, two-sided 99.9% confidence intervals will be provided. For the efficacy assessments for the comparison between Arms 2 and 3, repeated confidence interval approach using a **Lan-DeMets alpha spending function with** O'Brien-Fleming-**type boundaries** for the efficacy interim looks is planned.

A Wilson confidence interval around SPR estimate will be provided for Group B, if the timing of the review warrants such look. If so, a two-sided 95% confidence interval will be provided. If an interim look occurs, no adjustment will be made to the type I error (alpha) for the final analysis, since Group B consists of a small, single-arm study to provide information on the SPR estimate with a reasonable precision.

10.6 Analyses

All study analyses will be conducted separately in Groups A and B, unless otherwise noted. A detailed SAP will be developed before clinical trial initiation. The following provides a brief description of analyses that address the primary and secondary objectives. All available data on participants who initiated the vaccination series will be analyzed.

10.6.1 Group A

<u>Primary Outcome Analyses on Vaccine Response</u>
For each of the two primary objectives on vaccine response, the primary outcome on the SPR at 8 weeks after the two-dose vaccination series (Arm 1, week 12) and at 4 weeks after the three-dose vaccination series (Arms 2 and 3, week 28) will be analyzed as a binary variable. To preserve the overall type I error rate at 5%, a Bonferroni correction will be applied for two comparisons.

A two-sided 97.5% confidence interval will be provided for the estimated proportion difference between Arm 1 and Arm 3 (Arm 3 minus Arm 1). If an interim look with a 99.9% confidence interval occurs to assess potential harm, the alpha level for the final analysis will not be adjusted, since 0.1% alpha spending in the interim look would have minimal effect on the final confidence interval. A score-based approach similar to the Wilson method for proportion differences (known as Newcombe method) will be used to estimate a stratified confidence interval. If the resulting confidence interval lies entirely below the non-inferiority margin of 10%, then non-inferiority of Arm 1 compared to Arm 3 (control) will be concluded.

Superiority of Arm 1 compared to Arm 3 will be concluded if the confidence interval lies entirely below zero.

For the comparison between Arm 2 and Arm 3, a two-sided 97.5% stratified confidence interval will be provided for the estimated proportion difference between Arm 2 and Arm 3 (Arm 2 minus Arm 3). A score-based method of Newcombe will be used, accounting for stratified randomization. A repeated confidence interval approach using a **Lan-DeMets alpha spending function with an** O'Brien-Fleming **approach** that accounts for the repeated analyses due to interim monitoring will be provided. If the resulting confidence interval lies entirely above zero, then superiority of Arm 2 compared to Arm 3 (control) will be concluded.

For both comparisons, additional analyses may be conducted where missing SPR is imputed if both antibody results immediately prior to and after the missed visit are <10 mIU/mL, or if both are ≥10 mIU/mL.

Primary Analysis on Safety

To address the study objectives on safety, the proportion of participants with AEs will be summarized with a two-sided 95% confidence interval in each study arm using the Wilson method. The outcome in 10.2.1.2 will be used, and the worst graded event per participant over time will be used. In addition, proportion estimates at the end of study will be calculated using the Kaplan-Meier method with Greenwood's formula for the variance. Descriptive summaries of events and the number of participants experiencing the events will be provided by grade. All diagnoses reported as AEs will be described. The confidence intervals on AEs will be provided without adjustment for stratification factors. They will also be provided by sex, if there are sufficient numbers of events where such estimation is meaningful.

Secondary Outcome Analyses

The following secondary analyses on SPR will be conducted using a two-sided type I error rate of 2.5% without further correction for multiple analyses. This type I error was chosen to provide confidence intervals of widths comparable to the primary outcome analyses.

The SPR at additional study weeks will be analyzed as a binary variable. The SPR proportion will be estimated for each analysis group (study arm or combined study arms). A two-sided 97.5% confidence interval around the difference in proportions will be calculated using a score-based approach similar to the Wilson method (known as Newcombe method). These will also be stratified confidence intervals, similar to the primary analysis approach. The secondary objectives on the SPR comparisons will be addressed using this analysis approach.

For the secondary objectives on the analysis of the antibody titer as a continuous measure, a two-sided type I error rate of 5% without correction for multiple analyses will be used. The geometric mean titer will be calculated for each analysis group (study arm or combined study arms) and compared using a t-test. A two-sided 95% confidence interval around the difference in the geometric means will be calculated assuming t-distribution of log10-transformed antibody titer. The confidence intervals will be provided across stratification factors and within stratum.

To address the study objective on post-injection AEs, the proportion of participants with events will be summarized with a two-sided 95% confidence interval in each study arm using the Wilson method. For these analyses, the worst graded event per participant over the specified time after each injection will be used. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided. The confidence intervals on the post-injection events will be provided across stratification factors.

Furthermore, descriptive summaries will be provided on the participants who discontinue the vaccination series early, categorized by the reasons for discontinuation. Similar summaries will be provided on the participants who discontinue the study early.

While the study has not been powered for testing the sex or race effect on the success of HEPLISAV-B vaccination using the primary outcome, logistic regression models that include sex and race will be analyzed and reported as secondary analyses. Logistic regression models will also be used to assess other demographic or baseline clinical characteristics associated with vaccine response.

10.6.2 Group B

Primary Outcome Analysis on Vaccine Response

The primary outcome on the SPR at 4 weeks after the vaccination series will be assessed by estimating the proportion of participants who achieve SPR. A two-sided 95% confidence interval around the observed SPR proportion will be provided using the Wilson score method for binomial variables. If the confidence interval lies above 55%, then it will be concluded that the SPR proportion is

greater than 55%. If an interim look occurs, no adjustment will be made to the type I error (alpha) for the final analysis. Group B consists of a small, single-arm study to provide information on the SPR estimate with a reasonable precision.

Primary Analysis on Safety

To address the objective on safety, the proportion of participants with AEs will be summarized with a two-sided 95% confidence interval using the Wilson method. For Objective 1.2.4, the outcome described in 10.2.1.4 will be used. For the analysis, the worst graded event per participant over time will be used. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided by grade. Diagnoses reported as AEs will be described.

Secondary Outcome Analyses

Each secondary analysis will be conducted using a two-sided type I error rate of 5% without correction for multiple analyses.

The SPR at additional study weeks will be analyzed as a binary variable. A two-sided 95% confidence interval around the observed SPR proportion will be provided using the Wilson score method for binomial variables.

To address objectives related to antibody titer as a continuous measure, the geometric mean titers will be calculated with two-sided 95% confidence intervals, assuming t-distribution of $\log_{10}$-transformed antibody titer.

To address the study objective on post-injection AEs, the proportion of participants with events will be summarized with a two-sided 95% confidence interval using the Wilson method. For the analysis, the worst graded event per participant over the specified time will be used. In addition, descriptive tables summarizing the events and the number of participants experiencing the events will be provided. Diagnoses reported as AEs will be described.

Furthermore, descriptive summaries will be provided on the participants who discontinue the vaccination series early, categorized by the reasons for discontinuation. Similar summaries will be provided on the participants who discontinue the study early.

While the study has not been powered for testing the sex or race effect on the success of HEPLISAV-B vaccination using the primary outcome, the proportions of subgroups defined by sex and race who achieve the primary outcome will be estimated with confidence intervals and reported as secondary analyses.

11.0 PHARMACOLOGY PLAN

Not applicable.

12.0 DATA COLLECTION AND MONITORING

12.1 Records to Be Kept

Electronic case report form (eCRF) screens will be made available to sites for data entry. Participants must not be identified by name on any data submitted to the DMC. Participants will be identified by the patient identification number (PID) and study identification number (SID) provided by the ACTG DMC upon randomization/registration.

12.2 Role of Data Management

12.2.1 Instructions concerning entering study data on eCRFs will be provided by the ACTG DMC. Each CRS is responsible for keying the data in a timely fashion.

12.2.2 It is the responsibility of the ACTG DMC to ensure the quality of computerized data for each ACTG study. This role extends from protocol development to generation of the final study databases.

12.3 Clinical Site Monitoring and Record Availability

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity [45]. The site must make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. The Data Management Center will configure Medidata Remote Source Review (RSR) and make it available to all sites. We encourage Sites to use the DMC provided Medidata RSR platform but other potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, and direct access to Electronic Medical Record (EMR). Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

12.4 Reporting Protocol Deviations

The site principal investigator and staff are responsible for identifying and reporting deviations. If protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations must be reported to the IRB/EC per their guidelines.

Refer to the MOPS for the definition of protocol deviation and instructions for completing the study protocol deviation eCRF.

13.0 PARTICIPANTS

13.1 Institutional Review Board (IRB) Review and Informed Consent

This protocol and the informed consent documents (Appendices I and II) and any subsequent modifications will be reviewed and approved by the IRB or EC responsible for oversight of the study. The informed consent will be obtained from the participant and documented as per the site's Informed Consent Process SOP. A signed consent form will be obtained from the participant (or legal guardian, or person with power of attorney for participants who cannot consent for themselves). The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the participant or legal guardian, and this fact will be documented in the participant's record.

13.2 Participant Confidentiality

All laboratory specimens, evaluation forms, reports, and other records that leave the site will be identified by coded number only to maintain participant confidentiality. All records will be kept locked. All computer entry and networking programs will be done with coded numbers only. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the ACTG, IRB/EC, FDA, NIAID, OHRP, other local, US, and international regulatory entities as part of their duties, or the industry supporter or designee.

13.3 Study Discontinuation

The study may be discontinued at any time by the ACTG, IRB/EC, FDA, NIAID, OHRP, other government agencies as part of their duties to ensure that research participants are protected, or the industry supporter.

14.0 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by ACTG policies. Any presentation, abstract, or manuscript will be made available for review by the industry supporter prior to submission.

15.0 BIOHAZARD CONTAINMENT

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

All dangerous goods and materials, including diagnostic specimens and infectious substances, must be transported using packaging mandated by CFR 42 Part 72. Please refer to instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

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APPENDIX I: SAMPLE INFORMED CONSENT

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

For protocol:
A5379 B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe): Evaluation of HEPLISAV-B

FINAL Version 3.0, 13Dec20222

SHORT TITLE FOR THE STUDY: BEe-HIVe

SUMMARY

PURPOSE

This is a research study and your participation in this study is voluntary. The purpose of this study is to find out whether a hepatitis B vaccine called HEPLISAV-B is more effective at preventing hepatitis B infection in adults living with HIV than the current standard hepatitis B vaccine called ENGERIX-B. Vaccine side effects will also be studied.

STUDY TREATMENT

There will be treatment provided in this study. Participants will receive either HEPLISAV-B or ENGERIX-B. Both vaccines are approved by the United States Food and Drug Administration (FDA). Each vaccine will be given as a shot (injection) in the muscle of your upper arm. Some participants in the study will receive two shots of HEPLISAV-B (the dosing approved by the FDA), some participants will receive three shots of HEPLISAV-B, which is an investigational (experimental) dosing schedule, and some participants will receive three shots of ENGERIX-B (the dosing approved by the FDA). You will continue taking your anti-HIV medications that are prescribed by your doctor while you are in this study. The anti-HIV medications will not be provided to you in this study.

NUMBER OF PARTICIPANTS

There are two treatment groups of people, for a total of 634 participants.

LENGTH OF STUDY

Participants will be on study for 72 weeks (almost 1.5 years). Overall, you may have up to 10 study visits.

REQUIRED ACTIVITIES

Blood collections

At all visits, some blood will be collected from a vein in your arm.

- At all visits, your blood will be stored.

Special procedures
- At 2 or 3 visits, you will have a vaccine shot.
- You will be contacted by telephone, text message, or e-mail throughout the study.

RISKS

The following are possible:
- Pain, soreness, redness, swelling, and hardening where you had your vaccine shot.
- Fainting, fatigue, dizziness, headache, generally not feeling well, fever, and muscle pain.
- Allergic reaction including fever, chills, headache, rash, itchy skin, low or high blood pressure, or difficulty breathing.
- Risks related to blood draws and social harm.

BENEFITS

If you take part in this study, there may be a direct benefit to you if you respond to either vaccine. It is also possible that you receive no benefit from being in this study.

OTHER CHOICES

Instead of being in this study you have the choice of receiving approved HBV vaccine as part of regular care from your doctor or participating in and receiving a different experimental HBV vaccine, if you qualify.

INTRODUCTION

You are being asked to take part in this research study because you are living with human immunodeficiency virus (HIV) (the virus that causes AIDS). This study is sponsored by the National Institutes of Health (NIH). The doctor in charge of this study at this site is: (insert name of Principal Investigator). Before you decide if you want to be a part of this study, we want you to know about the study.

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. 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?

This study is looking at hepatitis B virus (HBV) vaccination in adults 18 to 70 years of age living with HIV around the world. Hepatitis B is a serious viral infection that affects the liver and is transmitted through blood and body fluids. A vaccine (a shot of medicine given through a needle) can prevent HBV, but vaccines are not used to cure HBV.

Vaccinating people living with HIV against HBV does not always work in preventing them from getting HBV, especially in people with weak immune systems or difficulty fighting infections. Prevention of HBV in individuals living with HIV has primarily been done by giving people three

shots over 6 months. A new vaccine approved by the United States Food and Drug Administration (FDA), called HEPLISAV-B, has been shown to provide a better response in people who have not responded well to the older HBV vaccines. The purpose of this study is to see whether this new vaccine, HEPLISAV-B, will be more effective in adults living with HIV than the current standard vaccine, ENGERIX-B also approved by the FDA. Some participants in the study will receive two shots of the HEPLISAV-B vaccine (the dosing approved by the FDA), some participants will receive three shots of the HEPLISAV-B vaccine (an (investigational [experimental] dosing schedule), and some participants will receive three shots of ENGERIX-B (the dosing approved by the FDA). Vaccine adverse reactions (side effects) will also be studied.

WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?

There are two groups of individuals in this study. One group will include individuals who have received a previous HBV vaccination but did not respond well to the vaccine (Group A). The other group will include individuals who have never received a HBV vaccination (Group B). If you are in Group A, you have an equal chance of receiving either two shots of HEPLISAV-B, three shots of HEPLISAV-B, or three shots of ENGERIX-B (current standard HBV vaccine). You will not be able to choose which of these three options you will receive during this study; however, you and the study staff will know which vaccine dose you are receiving. If you are in Group B, you will receive three shots of HEPLISAV-B. Each vaccine will be given as a shot (injection) in the muscle of your upper arm. You will continue taking your anti-HIV medications that are prescribed by your doctor while you are in this study. The anti-HIV medications will not be provided to you in this study.

Screening
If you would like to be in this study, after you have read and signed this informed consent form, you will come to the clinic for a screening visit to make sure you meet the requirements for joining the study. This visit will take about 1 hour. At this visit:

- Your HIV status will be confirmed.
- You will be asked questions about your medical history and any medications you are taking or have taken in the past.
- You will have a complete physical exam, including vital signs (temperature, pulse, respiration rate, and blood pressure).
- You may be tested to see if you have HBV.
- You may have approximately **42** mL (about **3** tablespoons) of blood collected (refer to Attachment A for more details).
- You will decide if you want to participate in an optional visit that will occur within 16-28 hours after your first vaccine shot. *[For non-US sites: remove]*

Information Collected at Screening
There is some information that we collect on everyone who is screened for an ACTG study. As part of your screening visit, some demographic (for example, age, gender, race), clinical (for example, disease condition, diagnosis), and laboratory (for example, CD4+ cell count, viral load) information will be collected from you. We also collect information on whether you use (or have used) IV drugs.

We will collect this information even if you do not enroll in this study. This information is collected so that ACTG researchers may help determine whether there are patterns and/or common reasons why people do not join a study.

Entry
If you are eligible for the study and still interested in participating, you will come in for the entry visit. This visit will take about 1.5 hours. At this visit:

- You will be asked questions about your medical history and any medications you are taking or have taken in the past.
- You will have a brief physical exam.
- You may have approximately 1**35** mL (about **9** tablespoons) of blood collected (refer to Attachment A for more details).
- Your blood will be stored for testing at the end of the study.
- If you are able to get pregnant, some of your blood or urine will be collected to test for pregnancy. If the pregnancy test is positive, you will not proceed with entry into the study and not receive the vaccine.
- You will either receive one shot of HEPLISAV-B or ENGERIX-B.
- You will take home a diary card.

Optional visit after your first vaccine shot *[For non-US sites: remove this visit]*
This visit will only be for some participants in Group A, and is optional. After your first vaccine shot, you may come back within 16-28 hours for another visit the next morning. This visit will take about 30 minutes. At this visit:

- You will have approximately 105 mL (7 tablespoons) of blood collected (refer to Attachment A for more details).

Other Study Visits
You will be asked to come in up to 8 more times throughout the study. These visits will last about 1 hour. At most of these visits:

- You will have a brief physical exam.
- You will have as little as **5** mL (**about** 1 teaspoon) to as much as **132** mL (**9** tablespoons) of blood collected at any one visit (refer to Attachment A for more details).
- If you are able to become pregnant, you will have a pregnancy test **and the result must be negative within 2 days prior to receiving a study vaccine dose. You will also have a pregnancy test** at your last study visit. Options about staying on the study if you become pregnant are explained elsewhere in the consent.
- Your blood will be stored for testing at the end of the study. Some participants in Group A will have extra blood stored.
- If you are receiving three shots of HEPLISAV-B, you will receive one shot at two of these visits.
- If you are receiving three shots of ENGERIX-B, you will receive one shot at two of these visits.
- If you are receiving two shots of HEPLISAV-B, you will receive one shot at one of these visits.

- Site staff will remind you that it is important that you receive all the shots. It will improve your chance of responding to the vaccine.
- At the visits when you receive the vaccination, you will be given a diary card.
- You will bring the diary card back to the clinic at the visit after the vaccination.
- You will be contacted by the study staff a few times between visits.

Remote Data Collection

Sometimes the study staff may need to conduct a scheduled visit with you remotely (for example, by telephone, or via telehealth). This could happen for any of the reasons listed below:

- **You are not able to attend a visit in person (for example, because you are not feeling well or you are in lockdown or quarantine).**
- **The site is temporarily unable to conduct non-essential visits in the clinic (for example, because of a problem at the facility or because of a public health emergency).**

Regardless of the reason, the study staff will attempt to contact you and obtain as much of the required information from you as is possible. Further, the in-person visit will be rescheduled.

Details of how often the study visits will occur and information about the procedures are explained in Attachment A, as part of this consent.

CAN I CHOOSE THE TYPES OF RESEARCH THAT MY SAMPLES AND INFORMATION ARE USED FOR?

Some of your blood will be stored and used for study-required (immunologic, virologic, and standard genetic) testing.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you. If you are enrolling in this study at a site outside the US, you must know that biologic samples collected from you may be shipped and stored outside of the country from which they are collected.

The testing described above (immunologic, virologic, and genetic) is required by this study. If you do not agree to the storage or testing that has been described above, you cannot join this study.

Please refer to Attachment B to consent for use of your samples in other studies.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 634 people will take part in this study.

HOW LONG WILL I BE IN THIS STUDY?

You will be in this study for about 72 weeks (almost 1.5 years).

WHY WOULD THE DOCTOR TAKE ME OFF THIS STUDY EARLY?

The study doctor may need to take you off the study early without your permission if:
- The study is stopped or cancelled
- A Data and Safety Monitoring Board (DSMB) recommends that the study be stopped early (A DSMB is an outside group of experts who monitor the study.)
- You are not able to start the study vaccine

The study doctor may also need to take you off the vaccination series without your permission if:
- You have an allergic reaction or other severe reaction to either of the study vaccines
- You have a new or worsened immune-mediated adverse event. These may include conditions such as gastrointestinal, liver, metabolic, musculoskeletal, neuroinflammatory, and skin disorders and vasculitides. Study staff can tell you about these.
- You need a treatment that you may not take while getting the vaccine you have been assigned to take.
- **If you miss the 2nd dose in the allowed timeframe for a two-dose series.**
- **If you miss the 3rd dose in the allowed timeframe for a three-dose series.**

If you must stop the study vaccine before the study is over, the study doctor may ask you to continue to be part of the study and return for some study visits and procedures.

<u>If I have to permanently stop the study-provided vaccine before completing/receiving all doses, or once I leave the study, how would the vaccine be provided?</u>
During the study:

If you must permanently stop the study-provided vaccine before completing/receiving all doses, the study staff will discuss other options that may be used to complete your vaccination.

After the study:

If you completed all the vaccine shots, receiving more shots would not be necessary. If you do not finish the vaccine series during the study and this would be of benefit to you, the study staff will discuss how you may be able to obtain the vaccine.

WHAT ARE THE RISKS OF THE STUDY?

The vaccines used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these vaccines. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study vaccine side effects, please ask the medical staff at your site.

There is a risk of serious and/or life-threatening side effects when non-study medications are taken with the study vaccines. For your safety, you must tell the study doctor or nurse about all medications you are taking before you start the study and also before starting any new medications while on the study. Also, you must tell the study doctor or nurse before enrolling in any other clinical trials while on this study.

Before it was approved by the FDA, HEPLISAV-B was tested in more than 9500 people. Overall, the side effects were similar to the side effects seen with other vaccines. In one study, people who got HEPLISAV-B had a heart attack more often than people who got ENGERIX-B. However, the heart attacks were rare. After careful review by experts, no relationship between the heart attacks and HEPLISAV-B was found. Since FDA approval, Dynavax, the manufacturer of HEPLISAV-B, has been conducting a large observational study of 30,000 people who received HEPLISAV-B and 30,000 people who received ENGERIX-B to evaluate heart attacks and the theoretical concern that vaccines can cause autoimmune disease (a condition in which the immune system mistakenly attacks the body). **The final** study results showed no relationship between heart attacks and HEPLISAV-B.

<u>Vaccine-related Hypersensitivity (allergic reaction)</u>
Fever
Chills
Headache
Rash
Itchy skin
Low or high blood pressure
Difficulty breathing

<u>Related to Vaccine Injections (shots)</u>
Injection site pain
Injection site soreness
Redness around the injection site
Injection site hardening/mass
Injection site swelling
Fainting

<u>HEPLISAV-B Risks</u>
Fatigue
Headache
Malaise (generally not feeling well)
Fever
Muscle pain

<u>ENGERIX-B Risks</u>
Fatigue
Dizziness
Headache
Fever

Risks of Blood Draws
Taking blood may cause some discomfort, bleeding, bruising, and/or swelling where the needle enters the body, lightheadedness, and in rare cases, fainting, or infection.

Risks of Social Harm
It is possible that participating in this study will make it difficult for you to keep your HIV status secret from people close to you. This may lead to unwelcome discussions about or reactions to your HIV status. Please talk with the study staff if you have any concerns about this.

ARE THERE RISKS RELATED TO PREGNANCY?

At this time there are no studies done in humans that show that HEPLISAV-B is safe for unborn babies; information gathered on **people** who received the vaccine whilst pregnant is not enough to figure out if it is safe for the unborn babies. Studies done in animals have not shown any such harms. If you are having sex that could lead to pregnancy, you must take precautions to not become pregnant.

If you can become pregnant, you and your partner must use reliable birth control that you can discuss with the study staff. At least one of the following methods MUST be used for the duration of the study:
- Condoms (male or female) with or without a spermicide
- Diaphragm or cervical cap with spermicide
- Intrauterine device (IUD)
- Hormone-based contraceptive

If you can become pregnant, you must have a pregnancy test before you enter this study and a few times during the study. These tests must show that you are not pregnant. If you think you may be pregnant at any other time during the study, tell your study staff right away. The study staff will talk to you about your choices.

It is not known if HEPLISAV-B or ENGERIX-B, pass through breast milk. Therefore, breastfeeding individuals will not be enrolled in this study.

WHAT IF I BECOME PREGNANT DURING THE STUDY?

If you become pregnant during the study, you will have the option to stay in the study and either continue the vaccination series or not continue. Before you decide what you want to do, the study staff will counsel you about your options and the risks involved. You will need to complete a separate Pregnancy Consent Form to stay in the study and continue with the vaccination series.

If you become pregnant while on study, the study staff would like to obtain information from you about the outcome of the pregnancy (even if it is after your participation in the study). If you are taking anti-HIV drugs when you become pregnant, your pregnancy will be reported to an international database that collects information about pregnancies in **people** taking anti-HIV

drugs. This report will not use your name or other information that could be used to identify you.

You may volunteer to participate in the HEPLISAV-B pregnancy registry. Information that could identify you will be collected in that registry if you choose to enroll. You may call 1-844-443-7734 to find out more about this registry. *[For non-US sites: remove information about HEPLISAV-B pregnancy registry]*

For individuals who can become pregnant:

____ (initials) I agree for my information to be included in the HEPLISAV-B pregnancy registry if I become pregnant. *[For non-US sites: remove]*

OR
____ (initials) I do not want to be included in the HEPLISAV-B pregnancy registry if I become pregnant. *[For non-US sites: remove]*

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

If you take part in this study, there may be a direct benefit to you if you respond to the vaccine. This means you will be protected from getting HBV, but no guarantee can be made. It is also possible that you may receive no benefit from being in this study. Information learned from this study may help others who have HIV and HBV.

WHAT OTHER CHOICES DO I HAVE BESIDES THIS STUDY?

Instead of being in this study you have the choice of:
- Receiving approved HBV vaccine as part of regular care from your doctor
- Participating in and receiving a different experimental HBV vaccine, if you qualify

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits of these choices.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, this research is covered by a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site), institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on **https://www**.ClinicalTrials.gov, as required by U.S. **L**aw. This **W**eb **s**ite will not include information that can identify you. At most, the **W**eb **s**ite will include a summary of the results. You can search this **W**eb **s**ite at any time.

For Sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. In addition to the efforts of the study staff to help keep your personal information private, this research is covered by a Certificate of Confidentiality from the US Federal Government. The Certificate of Confidentiality may not provide protections for your data in your country. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the U.S. Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties (insert name of site), institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on **https://**ClinicalTrials.gov, as required by U.S. **L**aw. This **W**eb **s**ite will not include information that can identify you. At most, the **W**eb **s**ite will include a summary of the results. You can search this **W**eb **s**ite at any time.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

WHAT ARE THE COSTS TO ME?

Taking part in this study may lead to added costs to you and your insurance company. In some cases, it is possible that your insurance company will not pay for these costs because you are taking part in a research study. The study vaccine will be provided at no cost during this study.

WILL I RECEIVE ANY PAYMENT?

[Insert site-specific information on compensation to study participants.]

WHAT HAPPENS IF I AM INJURED?

If you are injured as a result of being in this study, you will be given immediate treatment for your injuries.

[*Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry Clinical Trials Insurance (CTI), this must be indicated in the informed consent.]* ***Please note that, for <u>all sites</u> (not as part of an either/or statement with CTI), the NIH does not have a mechanism to provide direct compensation for research-related injury.***

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.* ***OR***
- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH****, regardless of whether CTI is available****.*

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

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Taking part in this study is completely voluntary. You may choose not to take part in this study or leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. At the end of the study, you will be told when study results may be available and how to learn about them. Individual results related to your safety and significant clinical findings requiring medical attention and follow up will be provided to you and your treating medical provider.

If you do not have the capacity to consent, your legally authorized representative may consent on your behalf. During the course of the study, if you become able to consent, informed consent

will be obtained from you. At that time you can decide whether you want to stay in the study or not.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:
- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Number of above

SIGNATURE PAGE

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.

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Participant's Legally Authorized Representative (print) (As appropriate)	_____ Legally Authorized Representative Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff's Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date

ATTACHMENT A: STUDY VISITS AND PROCEDURES

Section A: Study Visits

Table 1: Expected Study Visit Schedule for Participants Receiving Three Shots of a Vaccine

Procedure	Screening	Entry	On-study (visit weeks)								End Study Early
			1st visit after 1st vaccine shot*	4	8	12	24	28	32	48	72	
HIV confirmed	✓			Not applicable								
Questions about your health and medications you are taking	✓	✓		**At all visits**								✓
Physical exam	✓	✓		At all visits								✓
Blood collected	✓	✓	✓	At all visits								✓
Pregnancy test		✓		At a few visits								✓
Blood stored		✓	✓	At all visits								✓
HEPLISAV-B vaccine		✓		At two study visits								
ENGERIX-B vaccine		✓		At two study visits								
Observation after vaccine		✓		At two visits								
Diary card given to you		✓		At two visits								
Bring diary card back to clinic				At a few visits								
Telephone, text message, or e-mail contact				Between a few visits								

*1st visit after 1st vaccine shot is only for some participants and is optional *[For non-US sites: remove this visit from the table and this footnote.]*

Table 2: Expected Study Visit Schedule for Participants Receiving Two Shots of a Vaccine

Procedure	Screening	Entry	On-study (visit weeks)							End Study Early
			4	8	12	24	28	52	72	
HIV confirmed	✓		Not applicable							
Questions about your health and medications you are taking	✓	✓	**At all visits**							✓
Physical exam	✓	✓	At all visits							✓
Blood collected	✓	✓	At all visits							✓
Pregnancy test		✓	At a few visits							✓
Blood stored		✓	At all visits							✓
HEPLISAV-B vaccine		✓	At one visit							
Observation after vaccine		✓	At one visit							
Diary card given to you		✓	At one visit							
Bring diary card back to clinic			At a few visits							
Telephone, text message, or e-mail contact			Between a few visits							

Section B: Explanation of Visit Schedule

Screening: This visit will take place not more than 45 days before you enter the study.

Entry: This visit will take place at least 24 hours after your screening visit.

On-study:
First visit after your first vaccine shot: This visit is optional. You will have blood collected and stored. This visit will take place the next day after you receive your first vaccine shot. Not all participants will have to do this visit. *[For non-US sites: remove this visit.]*

Next 72 weeks after study entry: you will have up to 10 study visits. You will continue to take your anti-HIV medications, which are not provided by the study.

Week 72 visit: This will be your final study visit.

Section C: Explanation of Procedures

Physical exam: You will have a complete physical exam at screening and then only a brief physical exam at other visits.

Blood collected: Blood will be collected from a vein in your arm at all visits for research tests that may include liver function tests, your HIV viral load (a measure of the amount of HIV in your blood), your CD4+ T-cell count (a measure of the strength of your immune system, the system that helps your body fight infections), HBsAb (a measure of how much HBV antibodies are in your body), and standard genetic testing. You will also have your blood stored at most visits. Some participants in Group A will have extra blood stored.

Pregnancy test: If you are able to become pregnant, you will have a pregnancy test, using either a blood sample or a urine sample. A pregnancy test will be done a few times throughout the study and any time you think you may be pregnant.

HEPLISAV-B or ENGERIX-B vaccination: You will have either three shots total of HEPLISAV-B or ENGERIX-B at three different time points (when you enter the study and 4 and 24 weeks after) or two shots total of HEPLISAV-B at two different time points (when you enter the study and 4 weeks after). Each vaccine will be given as a shot in the muscle of your upper arm. During these visits, you will be observed for 30 minutes after the shot in case you have a reaction to the shot. Your temperature will be measured.

Diary card: You will be provided with a diary card, a ruler, and a thermometer at the visits you receive the vaccination. You will take the diary card home. For 7 days after you receive the vaccination, you will record any reactions you had to the vaccine (pain, redness, or swelling near where you had the shot, not feeling well, headache, body aches, and feeling tired). You will also measure and record your temperature in the evenings. You will be asked to bring the diary card back to the clinic at your next visit.

Telephone, e-mail, or text message contact: You will be contacted by telephone, text message, or e-mail to remind you to complete the diary card and to bring it to your next study visit.

ATTACHMENT B: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

When samples are no longer needed for this study, the ACTG may want to use them in other studies and share them with other researchers. These samples are called “extra samples.” The ACTG will only allow your extra samples to be used in other studies if you agree to this. If you have any questions, please ask.

Identifiers will be removed from your samples and from any private information that has been collected about you. This means that no one looking at the labels or at other information will be able to know that the samples or information came from you.

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

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

When a researcher wants to use your samples and information, his or her research plan must be approved by the ACTG. Also, the researcher’s institutional review board (IRB) or ethics committee (EC) will review the plan. *[Site: If review by your institution’s IRB/EC/RE is also required, insert a sentence stating this.]* IRBs/ECs protect the rights and well-being of people in research. If the research plan is approved, the ACTG will send your samples to the researcher’s location. This means that researchers who are not part of the protocol team may use your samples without asking you again for your consent.

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

You may withdraw your consent for research on your extra samples at any time, and the specimens will be discarded.

Please choose the response that matches what you want by putting your initials in the space provided. Please ask the staff any questions that you have before you indicate your selection.

<u>Research without Human Genetic Testing</u>
If you agree, your extra samples may be stored (with usual protection of your identity) and used for ACTG-approved HIV-related research that does not include human genetic testing.

____ (initials) I understand and I agree to this storage and possible use of my samples.

OR
____ (initials) I understand but I do not agree to this storage and possible use of my samples.

Research with Human Genetic Testing

The ACTG has two different studies that collect samples for genetic testing.

If you live in the US, this study is called ACTG A5128, Plan for Obtaining Informed Consent to Use Stored Human Biological Materials (HBM) for Currently Unspecified Analyses.

If you live outside of the US, this study is called ACTG A5243, Plan for Obtaining Human Biological Samples at Non-US Clinical Research Sites for Currently Unspecified Genetic Analyses.

Your site might ask you if you would like to participate in one of these studies if it is being done where you live. If you would like to participate, you will sign a separate consent form.

Your extra samples will not be used for human genetic testing unless you sign and date a consent form for A5128 or A5243.

APPENDIX II: SAMPLE INFORMED CONSENT FOR **PARTICIPANTS** WHO BECOME PREGNANT WHILE ON STUDY

DIVISION OF AIDS
AIDS CLINICAL TRIALS GROUP (ACTG)

For protocol:
A5379 B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe): Evaluation of HEPLISAV-B

FINAL Version 3.0, 13Dec20222

SHORT TITLE FOR THE STUDY: BEe-HIVe

SUMMARY

PURPOSE	Because you are pregnant, you are being asked if you want to continue to take part in this research study.
STUDY TREATMENT	Treatment required is the same as the treatment stated in the main study A5379/BEe-HIVe consent form.
NUMBER OF PARTICIPANTS	There are two treatment groups of people, for a total of 634 participants.
LENGTH OF STUDY	Participants will be on study for 72 weeks (almost 1½ years). You will continue to have study visits and tests as stated in the main study A5379/BEe-HIVe consent form.
REQUIRED ACTIVITIES	The activities required are the same as the ones stated in the main study A5379/BEe-HIVe consent form.
RISKS	The following risks are possible: • Your body could respond differently to vaccines since you are pregnant. • There is no information on whether HEPLISAV-B poses a risk of harm to **people who are** pregnant or their unborn children. Animal studies suggest no such risk, but the results may not apply to humans.

- ENGERIX-B has been widely used in pregnancy, and the available information does not suggest that it poses a risk of harm to **people who are** pregnant or their unborn children.

BENEFITS Continuing in the study and finishing your vaccination series may improve your chances of responding to the vaccine. This may be of benefit to you and your baby, but no guarantee can be made.

OTHER CHOICES Instead of being in this study, you have the choice of discontinuing the vaccination series.

INTRODUCTION

Because you are now pregnant, you are being asked if you want to continue taking part in this research study. This study was designed so that **people** who were pregnant could not join the study. However, because you were already in the study when you became pregnant, you will be allowed to stay in the study whether you choose to continue the study vaccination during your pregnancy or not.

This is a consent form. It gives you more information about this study and how it may affect your pregnancy and your baby. The study staff will talk with you about this information. You are free to ask questions about this study at any time. You may also talk with your own doctor about what is best for you and your baby. If you agree to stay in this study, you will be asked to sign this consent form. You will get a copy to keep.

WHAT DO I HAVE TO DO IF I STAY IN THIS STUDY?

If you choose to stay in this study, you will continue to have study visits and tests as stated in the main study A5379/BEe-HIVe consent form.

You have the option to continue the study vaccine series (either HEPLISAV-B or ENGERIX-B).

Care related to your pregnancy, the delivery of your baby, or the care of your baby will not be provided by this study. You must arrange for your care and your baby's care outside of this study.

Long-term follow-up is recommended for a baby whose mother takes anti-HIV drugs during pregnancy. The study staff will talk with you about long-term follow-up and the possibility of enrolling your baby in a long-term follow-up study.

WHAT ARE THE RISKS RELATED TO STAYING IN THE STUDY?

Now that you are pregnant, there are some possible risks you should know. These possible risks to you and your unborn baby are in addition to the risks that are described in the A5379/BEe-HIVe study consent you already signed.

Risks to You and Your Unborn Baby if Staying on HEPLISAV-B or ENGERIX-B
Your body could respond differently to vaccines since you are pregnant.

HEPLISAV-B
There is no information on whether HEPLISAV-B poses a risk of harm to **people who are** pregnant or their unborn children. Animal studies suggest no such risk, but the results may not apply to humans.

ENGERIX-B
ENGERIX-B has been widely used in pregnancy, and the available information does not suggest that it poses a risk of harm to **people who are** pregnant or their unborn children.

ARE THERE BENEFITS TO STAYING IN THIS STUDY?

If you continue to take part in this study, there may be a benefit to you and your baby, but no guarantee can be made. If you respond to the vaccine and become protected from infection with HBV, you can pass some of this protection to your baby until he or she builds up his or her own immunity. It is also possible that you and your baby will receive no benefit from continuing in this study. Information learned from this study may help others living with HIV.

WHAT OTHER CHOICES DO I HAVE BESIDES STAYING ON THE VACCINATION SERIES?

Instead of staying on the vaccination series, you have the choice of discontinuing the vaccination series.

Please talk to your doctor about these and other choices available to you. Your doctor will explain the risks and benefits.

WHAT ABOUT CONFIDENTIALITY?

For Sites in the US
We will do everything we can to protect your privacy. In addition to the efforts of the study staff to help keep your personal information private, this research is covered by a Certificate of Confidentiality from the US Federal Government. This certificate means that researchers cannot be forced to tell people who are not connected with this study, such as the court system, about your participation. Also, any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the US Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties *[insert name of site],* institutional review board (IRB) (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study.

Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

For Sites outside the US
Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. In addition to the efforts of the study staff to help keep your personal information private, this research is covered by a Certificate of Confidentiality from the US Federal Government. The Certificate of Confidentiality may not provide protections for your data in your country. Any publication of this study will not use your name or identify you personally.

Your records may be reviewed by the US Food and Drug Administration (FDA), the ACTG, the U.S. Office for Human Research Protections (OHRP), or other local, US, and international regulatory entities as part of their duties *[insert name of site],* institutional review board (IRB) or Ethics Committee (a committee that protects the rights and safety of participants in research), National Institutes of Health (NIH), study staff, study monitors, drug companies supporting this study, and their designees. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to yourself or others, we will be required to tell the proper authorities.

A description of this clinical trial will be available on ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

All information collected about you as part of the study will be sent securely to the ACTG statistical and data management center in the United States for combining with information from other study participants and statistical analysis of study results. Your name and other personal identifiers will not be sent. Your research site is responsible for sending your information in accordance with the laws, regulations, and policies of your country and research site.

WHAT ARE THE COSTS TO ME?

In addition to any costs that are described in the study consent you already signed, this study will not cover any cost related to your pregnancy, delivery of your baby, or care of your baby.

WHAT HAPPENS IF MY BABY OR I AM INJURED?

If your baby or you are injured as a result of being in this study, you will both be given immediate treatment for your injuries.

[*Sites: Please modify (if necessary) and insert one of these two statements, as appropriate to your site. If your site is required to carry Clinical Trials Insurance (CTI), this must be indicated in the informed consent.]* ***Please note that, for <u>all sites</u> (not as part of an either/or statement with CTI), the NIH does not have a mechanism to provide direct compensation for research-related injury.***

- *This site has clinical trials insurance. This insurance will allow the site to provide you with monetary compensation if you suffer harm as a result of participating in this research study.* ***OR***
- *The cost for this treatment will be charged to you or your insurance company. There is no program for compensation either through this institution or the NIH****, regardless of whether CTI is available****.*

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

WHAT ARE MY RIGHTS AS A RESEARCH PARTICIPANT?

Continuing to take part in this study is completely voluntary. You may choose not to continue in this study or you may leave this study at any time. Your decision will not have any impact on your participation in other studies conducted by NIH and will not result in any penalty or loss of benefits to which you are otherwise entitled.

We will tell you about new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. At the end of the study, you will be told when study results may be available and how to learn about them. Individual results related to your safety and significant clinical findings requiring medical attention and follow up will be provided to you and your treating medical provider.

____ (initials) I agree to stay in the study and continue receiving study vaccine series.

OR

____ (initials) I will stop study vaccine.

WHAT DO I DO IF I HAVE QUESTIONS OR PROBLEMS?

For questions about this study or a research-related injury, contact:
- Name of the investigator or other study staff
- Telephone number of above

For questions about your rights as a research participant, contact:
- Name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site
- Telephone number of above

SIGNATURE PAGE

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

_____ Participant's Name (print)	_____ Participant's Signature and Date
_____ Participant's Legally Authorized Representative (print) (As appropriate)	_____ Legally Authorized Representative Signature and Date
_____ Study Staff Conducting Consent Discussion (print)	_____ Study Staff's Signature and Date
_____ Witness's Name (print) (As appropriate)	_____ Witness's Signature and Date