ACTG NETWORK COORDINATING CENTER
Social & Scientific Systems, Inc., a DLH Holdings Company
8757 Georgia Avenue, 12th Floor
Silver Spring, MD 20910-3714
Phone: 301-628-3000

VERSION 2.0 LETTER OF AMENDMENT #1

DATE: February 18, 2022

TO: ACTG CTU Principal Investigators, CRS Leaders, and CTU/CRS Coordinators

FROM: A5379 Protocol Team

SUBJECT: Letter of Amendment #1 for Version 2.0 Protocol A5379

The following information affects the A5379 study and must be forwarded to the institutional review board (IRB)/ethics committee (EC) responsible for oversight of the study as soon as possible for their information and review. This Letter of Amendment (LOA) must be approved by the IRB/EC before implementation.

The following information affects the Sample Informed Consent. Your IRB/EC is responsible for determining the process of informing participants of the contents of this LOA.

Upon receiving final IRB/EC and any other applicable regulatory entity approvals for this LOA, sites should implement the LOA immediately. Sites are still required to submit an LOA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center. Sites will receive a registration notification for the LOA once the DAIDS PRO verifies that all required LOA registration documents have been received and are complete. A copy of the LOA registration notification, along with this letter and any IRB/EC correspondence, should be retained in the site's regulatory file.

This LOA is being implemented for the following reasons:

- To correct blood volumes listed in the sample informed consent.
- To note that trained study staff may administer the study vaccination.
- To add that changes in ART in the 28 days prior to study entry are allowed unless the change is due to ART toxicity.
- To add inactive or resolved cutaneous Kaposi sarcoma as an exception to exclusion criterion 4.4.7.
- To add that receipt of flu vaccine within 14 days prior to study entry is allowed.
- To add a complete history of COVID-19 vaccines to medication history.
- To allow remote data collection of post-entry evaluations due to illness or quarantine.
- To describe that COVID-19 vaccines are not prohibited on study.
- To clarify that pregnancy testing results must be negative within 2 days prior to the participant receiving study vaccine.
- To remove pregnancy testing at screening.
- To change "regardless of grade" to "Grade ≥1" for the following:
  a. Any concomitant medication associated with Grade ≥1 local and systemic injection reactions within 7 days after any study vaccine injection must be recorded on the eCRF.
  b. All Grade ≥1 local and systemic injection reactions within 7 days of any study vaccine injection must be recorded on the eCRF.
- To add a paragraph in Appendix I, Sample Informed Consent (WHAT ABOUT CONFIDENTIALITY?) now that the SDAC work in the ACTG is also covered by an approval from the Advarra IRB.
- To update language in Appendix I, Sample Informed Consent (WHAT HAPPENS IF I AM INJURED?)
- To add agreed-upon language from the ACTG Leadership Steering Committee in ATTACHMENT B, CONSENT FOR USE OF SAMPLES IN OTHER STUDIES.

- To update the Protocol Team Roster and Study Management sections.

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The following are changes (noted in bold or strikethrough) to A5379, Version 2.0, 07/01/20, titled, "B-ENHANCEMENT OF HBV VACCINATION IN PERSONS LIVING WITH HIV (BEe-HIVe): Evaluation of HEPLISAV-B." These changes will be included in the next version of the A5379 protocol if it is amended at a future date.

1. Protocol Signature Page

   A Protocol Signature Page (PSP) is appended for submission to the DAIDS Protocol Registration System (DPRS) as part of the LOA registration packet.

2. Protocol Team Roster

   a. The DAIDS Clinical Representative was replaced:

   DAIDS Clinical Representative
   ~~Leonard Sowah, MBChB, MPH, FACP~~
   ~~CCRB/TRP/DAIDS/NIAID/NIH/DHHS~~
   ~~Therapeutics Research Program~~
   ~~5601 Fishers Lane~~
   ~~Room 9F41~~
   ~~Rockville, MD 20852~~
   ~~Phone: 301-761-7231~~
   ~~Fax: 240-627-3107~~
   ~~E-mail: leonard.sowah@nih.gov~~
   Beverly L. Alston-Smith, MD
   DAIDS/NIAID/NIH/CCRB
   Complications and Co-Infectious Research Branch
   5601 Fisher Lane
   Room 9F50
   Rockville, MD 20852
   Phone: 301-435-3773
   E-mail: balston@niaid.nih.gov

   b. A second Data Manager has been added to the protocol team:

   Data Manager**s**
   Lillian Collins, MPH
   Frontier Science & Technology Research Foundation, Inc.
   4033 Maple Road
   Amherst, NY 14226
   Phone: 716-834-0900, Ext. 7308
   E-mail: collins@frontierscience.org

   c. The Industry Representative was replaced:

   Industry Representative
   Kelvin McKoy, MD, MBA
   Dynavax
   2100 Powell Street, Suite 900
   Emeryville, CA 94608

Phone: 202-271-0098
E-mail: kmckoy@dynavax.com
~~Randall Hyer, MD, PhD, MPH~~
~~Dynavax Technologies Corporation~~
~~2929 Seventh Street~~
~~Berkeley, CA 94710~~
~~Phone: 510-665-0451~~
~~E-mail: rhyer@dynavax.com~~

d. A second Laboratory Data Manager has been added to the protocol team:

Philip Marzinek, BS
Laboratory Data Manager
Frontier Science Foundation
Phone: 716-834-0900, Ext. 7399
4033 Maple Road
Amherst, NY 14226
E-mail: marzinek@frontierscience.org

e. The Laboratory Specialist was removed, and two new Laboratory Specialists have been added to the protocol team:

~~Rose Lagattuta~~
~~ACTG Laboratory Center at UCLA (ALC-UCLA)~~
~~11075 Santa Monica Boulevard~~
~~Suite 200~~
~~Los Angeles, CA 90025~~
~~Phone: 310-794-9979~~
~~E-mail: rlagattuta@milabcentral.org~~

Ceora Beijer, BS
ACTG Laboratory Center at UCLA (ALC-UCLA)
675 Charles E. Young Drive South
Los Angeles, CA 90095
Phone: 310-794-9052
E-mail: cbeijer@milabcentral.org

Sara Zabih, MS
ACTG Laboratory Center at UCLA (ALC-UCLA)
675 Charles E. Young Drive South
Los Angeles, CA 90095
Phone: 310-794-9084
Email: szabih@milabcentral.org

3. Study Management

Lillian Collins was added to the second and third bullet points under subsection Data Management:

- 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**).

4. Inclusion Criterion 4.1.2

   The criterion was updated as shown below:

   4.1.2 On ~~current~~ 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 is not allowed. For questions related to ART toxicity, sites should contact the team per the Study Management section.** ~~Individuals must not have changed ART within 56 days prior to study entry except for changes in integrase inhibitors, which will be allowed.~~

5. Exclusion Criterion 4.4.7

   The criterion was updated as shown below:

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

6. Exclusion Criterion 4.4.16

   The criterion was updated as shown below:

   4.4.16 Receipt of any inactivated virus vaccine within 14 days prior to study entry.

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

7. 5.3.1 HEPLISAV-B

   Study clinician was replaced with study staff in items 3 and 5 as shown below:

   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** ~~clinician~~ will determine the needle size depending upon the participant's deltoid muscle size.

   5. For the prefilled syringes, attach a sterile needle and administer intramuscularly. The study **staff** ~~clinician~~ 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.

8. 5.3.2 ENGERIX-B

   Study clinician was replaced with study staff in items 3 and 5 as shown below:

   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** ~~clinician~~ will determine the needle size depending upon the participant's deltoid muscle size.

   5. For the prefilled syringes, attach a sterile needle and administer intramuscularly. The study **staff** ~~clinician~~ 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.

9. 5.5.2 Prohibited Medications

   Clarification about COVID-19 administration was added as shown below:

   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 2nd or 3rd study vaccine dose, adjust the 2nd or 3rd 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.**

10. Table 6.1-1 Group A (Arm 1 only)

    Pregnancy testing at screening was removed as shown below:

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*		
Pregnancy Testing	~~X~~	X	X						X	X

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

Pregnancy testing at screening was removed as shown below:

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*		
Pregnancy Testing	~~X~~	X		X			X				X	X

12. Table 6.1-3 Group B Only

Pregnancy testing at screening was removed as shown below:

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*		
Pregnancy Testing	~~X~~	X	X			X				X	X

13. Table 6.3.3-1 Medication History

"COVID-19 vaccines" was added:

Table 6.3.3-1: Medication History

Medication Category	Complete History or Timeframe
Antiretroviral therapy	Within 60 days prior to entry
HBV vaccination1	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**
Prescription drugs for treatment of opportunistic infections	Within 60 days prior to entry

Medication Category	Complete History or Timeframe
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 antagonists2	Within 1 year except as noted below

14. 6.2.3 Post-Entry Evaluations

The following was added under the Missed Vaccination Visits section:

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 visits window, have the participant in as soon as possible for safety-related evaluations as an unscheduled visit, but 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 at Week 12 for Arm 1 in Group A, and Week 28 for Arms 2 and 3 in Group A and for Group B. 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.

15. 6.3.4 Clinical Assessments

a. A bullet point was added after “Inactivated or live virus vaccine” under the Concomitant Medications section as shown below:

- **Vaccines (experimental or standard of care, including COVID-19 vaccines and COVID-19 booster vaccines)**

b. The last bullet point under the Concomitant Medications section was updated as shown below:

- Any concomitant medication associated with **Grade ≥1** local and systemic injection reactions ~~regardless of grade,~~ within 7 days after any study vaccine injection.

16. 6.3.5 Laboratory Evaluations

Changes were made in the second and third sentences under Pregnancy Testing as shown below:

Pregnancy testing ~~must occur on the day of vaccination and the~~ result**s** must be negative **within 2 days** prior to the participant receiving HEPLISAV-B or ENGERIX-B. **Post-entry, n**~~N~~ote that a subsequent pregnancy test is not required for pregnant participants who consented to continue with the study.

17. 7.2 Adverse Event Collection Requirements for This Protocol

The fourth bullet point in the first paragraph of this section was updated as shown below:

- All **Grade ≥1** local and systemic injection reactions within 7 days of any study vaccine injection ~~regardless of grade~~.

18. APPENDIX I: SAMPLE INFORMED CONSENT, "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?"

The blood collection amounts under Screening, Entry, and Other Study Visits have been updated as follows:

Screening: The fifth bullet point has been revised to read:
- You may have approximately ~~34~~ **42** mL (about ~~2~~ **3** tablespoons) of blood collected

Entry: The third bullet point has been revised to read:
- You may have approximately ~~161~~ **135** mL (about ~~11~~ **9** tablespoons) of blood collected

Other Study Visits: The second bullet point has been revised to read:
- You will have as little as ~~3~~ **5** mL (**about** 1 teaspoon) to as much as ~~27~~ **132** mL (~~2~~ **9** tablespoons) of blood collected at any one visit

19. APPENDIX I: SAMPLE INFORMED CONSENT, "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?"

    The third bullet point under Other Study Visits has been updated as follows:

    - 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** ~~during the visits when you receive the vaccine and~~ at your last study visit. Options about staying on the study if you become pregnant~~,~~ are explained elsewhere in the consent.

20. APPENDIX I: SAMPLE INFORMED CONSENT, "WHAT DO I HAVE TO DO IF I AM IN THIS STUDY?"

    a. The following bullet point was removed under Screening as shown below:

       - ~~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 be able to join the study.~~

    b. The following was added under Other Study Visits as shown below:

    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.

21. APPENDIX I: SAMPLE INFORMED CONSENT, "WHAT ABOUT CONFIDENTIALITY?"

    The following paragraph was added as the fourth paragraph under For Sites outside the US:

    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.

22. APPENDIX I: SAMPLE INFORMED CONSENT, "WHAT HAPPENS IF I AM INJURED?"

The content was updated as shown below:

[*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 all sites (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**.*

23. ATTACHMENT A: STUDY VISITS AND PROCEDURES

a. Pregnancy testing was removed at screening in Table 1: Expected Study Visit Schedule for Participants Receiving Three shots of a Vaccine as shown below:

Procedure	Screening	Entry	On-study (visit weeks)								End Study Early
			1st visit after 1st vaccine shot*	4	8	12	24	28	32	48	72	
Pregnancy test	~~✓~~	✓		At a few visits								✓

b. Pregnancy testing was removed at screening in Table 2: Expected Study Visit Schedule for Participants Receiving Two shots of a Vaccine as shown below:

Procedure	Screening	Entry	On-study (visit weeks)							End Study Early
			4	8	12	24	28	52	72	
Pregnancy test	~~✓~~	✓	At a few visits							✓

24. ATTACHMENT B: CONSENT FOR USE OF SAMPLES IN OTHER STUDIES

The following section was updated as follows:

Research with Human Genetic Testing
~~Your extra samples will not be used for 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.

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

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

Principal Investigator: _____
Print/Type

Signed: _____ Date: _____
Name/Title