Letter of Amendment # 1 to:

HPTN 083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version 4.0, February 10, 2021
DAIDS Document ID: 20725
IND # 122, 744

Final Version of LoA # 1: 25 April 2021

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study, including the addendum study informed consent form, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete.

Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for HPTN 083.

If the HPTN 083 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in highlighted **bold** will be added, and text appearing in highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

Revision 1: A Protocol Signature Page is added per this LoA # 1.

Revision 2: Appendix V, Section A, 3d

Step 5: Participants Who Choose to Remain On or Switch To Oral TDF/FTC is modified to specify these participants will be followed for three years from enrollment or for one year since their last CAB injection, whichever is longer.

Revisions 3 a-e: Appendix V, Section C, Information in the Main Protocol that is Included Or Modified in Appendix V

a. A note for is added to Section C, Number 9 (Procedures for Suspected or Confirmed HIV Infection), for clarity regarding the visit schedule of these participants.

b. The incorrect table number is referenced in Section C, Number 11 (Hepatitis C). This is corrected.

c. Language is added to Section C, Number 15 (Human Subjects Considerations) that was inadvertently not included, with updates regarding compliance to 45 CFR 46.108(a)(4) and 21 CRF 56.108b.

d. Reference to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual is added to Section C, Number 15.

e. Language is added to Section C, Number 16 (Administrative Procedures), to reference the DAIDS SCORE Manual and to allow for remote monitoring. Protocol reference #93 is added to the main protocol.

Revisions 4 a-d: Appendix V, Section D, Schedules of Procedures and Evaluations for Steps 4 a-c and 5

a. Table 7, Step 4a: Footnote notations #2 and #3 are relocated and procedure descriptions from existing footnotes are added to the table for clarity.

b. Table 8, Step 4b: Procedure descriptions from existing footnotes are added to the table for clarity.

c. Table 9, Step 4c: Adherence counseling is removed from the Week 48 visit of this step. Procedure descriptions from existing footnotes are added to the table for clarity.

d. Table 10, Step 5: Footnote * is updated to specify participants will complete the procedures of this step for three years from the time of enrollment or for one year since their last injection of CAB, whichever is longer. Footnote notation #1 is relocated for consistency with the format of other tables. Footnote #7 is added to remove adherence counseling from the final visit of this step. Procedure descriptions from existing footnotes are added to the table for clarity.

Revisions 5 a-e: Appendix V, Section F, Addendum To The Main Sample Informed Consent Form

a. A new bullet is added for clarity regarding the visit schedule of participants who are HIV infected.

b. Language is added under "New Steps of the Study" to state that participants who previously were on CAB and are now currently taking TDF/FTC and choose to continue on TDF/FTC under Version 4.0 will be followed for one year following their last CAB injection. This is to "cover the tail" following the use of CAB, and this may require follow-up for longer than three years from the time

of enrollment. Participants will be followed in such situations either three years since enrollment or one year after their final injection (48 weeks after 8 weeks subsequent to final injection), whichever is longer.

c. General language is added under "Steps and Procedures" to allow for unforeseen circumstances requiring a shorter or longer period of follow-up not already outlined in the addendum consent form.

d. Under "Steps and Procedures," adherence counseling is removed from the Week 48 visit of Step 4c.

e. Under "Steps and Procedures," adherence counseling is removed from the final visit of Step 5.

IMPLEMENTATION

Revision 1 Protocol Signature Page

Protocol Signature Page

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

DAIDS Document ID # 20725
Version 4.0
February 10, 2021
Letter of Amendment # 1, 25 April 2021

I will conduct this 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.

Name of Investigator of Record	Signature of Investigator of Record	Date

Revision 2 **Appendix V, Section A, 3d, Step 5: Participants Who Choose to Remain On or Switch To Oral TDF/FTC**

Only the impacted portion of this section is depicted:

This Step is for participants who choose to remain on or switch to oral TDF/FTC. **Participants will complete the procedures of this step for three years from the time of enrollment or for one year since their last injection of CAB, whichever is longer.**

Revisions 3 a-e **Section C. Information in the Main Protocol that is Included Or Modified in Appendix V**

3a. **Number 9: Procedures for Suspected or Confirmed HIV Infection (from Section 5.14.2 of the main protocol, with modifications)**

Only the new note is depicted:

Note: Participants who became infected with HIV under Version 3.0 of the protocol and are being followed on the HIV infection quarterly visit schedule will complete their visits under this Version 4.0 amendment. For example, if they completed Weeks 0, 12, and 24 under Version 3.0 and Version 4.0 is now approved at the site, the participant will complete Weeks 36 and 48 under Version 4.0 and then be terminated from the study.

3b**. Number 11: Hepatitis C (from Section 5.16 of the main protocol, with modifications)**

Participants on Step 4c will have HCV antibody testing performed approximately annually (per Table ~~3~~ **9**). Incident HCV infection during follow-up will not mandate discontinuation of study product absent other requirements per Section E below - Toxicity Management.

3c. **Number 15: Human Subjects Considerations (from Section 8.0 of the main protocol, with modifications)**

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and must comply with the requirements of 45 CFR 46.108(a)(4) and 21 CFR 56.108b for promptly reporting the

following: all unanticipated problems involving risks to human subjects or others; serious or continuing noncompliance with applicable regulations or the requirements or determinations of their IRBs/ECs; and any suspension of termination of IRB approval.

Study sites will follow all applicable local and national requirements for required reporting and continual renewal of the protocol. Study sites are responsible for the submission of continuing review to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

3d. **Number 15: Human Subjects Considerations (from Section 8.0 of the main protocol, with modifications)**

Only the impacted paragraph from this section is depicted here:

Participants will document their provision of informed consent by signing their informed consent forms per site SOPs **(refer also to the DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual)**. Site-specific reimbursement amounts will be specified in the study informed consent forms. All participants will be offered a copy of their informed consent form.

3e. **Number 16: Administrative Procedures (from Section 10.0 of the main protocol, with modifications)**

Only the impacted paragraphs from this section are depicted here:

Implementation of Version 4.0 will be directed by Appendix V of this protocol as well as SSP Manual Appendix VIII. The SSP Manual includes links to the DAIDS ~~SOPs for Source Documentation and Essential Documents~~ **SCORE Manual**, Manual for Expedited Reporting of Adverse Events to DAIDS and the DAIDS Toxicity Tables.

Sites will continue to use the MediData Rave data management system. Quality control reports and queries routinely will be generated and distributed to the study sites for verification and resolution.

Study monitoring will continue to be performed as specified by and in accordance with DAIDS policies. Study monitors will:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

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.[93] The site will make available study documents

for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

For on-site visits, ~~S~~site investigators will **also** allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures, as applicable. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, ViiV Healthcare, Gilead Sciences, Inc., site IRBs/ECs, and other US, local, and international regulatory authorities. A site visit log will be maintained at each study site to document all visits (including virtual visits).

Only the new protocol reference is included below:

93. FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency: Guidance for Industry, Investigators, and Institutional Review Boards, March 2020, Updated on January 27, 2021. Accessed at: https://www.fda.gov/media/136238/download

Revisions 4 a-d

Only the impacted sections from these tables in Appendix V, Section D are depicted:

4a. **Table 7: STEP 4a Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections**

Procedures	DAY 0	WEEK 4
Interviewer-administered assessment (SMSQ)[4]	X	
CASI-administered assessment (behavioral assessment)[4]	X	
Chemistry testing[2] (creatinine only)	X[2]	X
Liver function tests[3] (AST, ALT, total bilirubin, alkaline phosphatase)	X[3]	X

FOOTNOTES FOR TABLE 7:
[2] The only chemistry required is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[3] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.
[4] Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered

4b. **Table 8: STEP 4b Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections**

Procedures*	DAY 0
Chemistry testing[5] (creatinine only)	X
Liver function tests[6] (AST, ALT, total bilirubin, alkaline phosphatase)	X

FOOTNOTES FOR TABLE 8:
[5] The only chemistry required is creatinine. If it was performed during Step 4a, do not perform at Day 0 of Step 4b
[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

4c. **Table 9: STEP 4c Schedule of Procedures and Evaluations – Cabotegravir Injections**

Procedures*	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Interviewer-administered assessment (SMSQ)[8]	X		X				X
CASI-administered assessment (behavioral assessment)[8]	X		X				X
Adherence counseling	X	X	X	X	X	X	~~X~~
Chemistry testing[5] (creatinine only)	X			X			X
Liver function tests[6] (AST, ALT, total bilirubin, alkaline phosphatase)	X			X			X

FOOTNOTES FOR TABLE 9
[5] The only required chemistry test is creatinine. If it was performed during Step 4a or 4b, do not perform at Day 0 of Step 4c.
[6] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.
[8] Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.

4d. **Table 10: STEP 5 Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC**

Procedures*	Day 0	*Weeks 12, 36 (60, 84, 108, 132, if required)	*Week 24, 48 (72, 96, 120, 144, if required)
Interviewer-administered assessment (SMSQ)[8]	X		X
CASI-administered assessment (behavioral assessment)[8]	X		X
Adherence counseling[7]	X	X	X
Urine collection for GC/CT testing and urinalysis[1]	X[1]		X
Rectal swab for GC/CT testing[1, 2]	X[1]		X
Syphilis serologic testing[1]	X[1]		X
Urine GC/CT testing[1]	X[1]		X
Rectal swab GC/CT testing[1]	X[1]		X
Chemistry testing[4] (creatinine only)	X		X
Liver function tests[5] (AST, ALT, total bilirubin, alkaline phosphatase)	X		X

FOOTNOTES FOR TABLE 10:

* **Participants will complete the procedures of this step for three years from the time of enrollment or for one year since their last injection of CAB, whichever is longer.** ~~Participants originally randomized to oral TDF/FTC who choose to continue TDF/FTC will be followed until three years from date of enrollment.~~ Contact the CMC for guidance for participants originally randomized to TDF/FTC who have been missing to follow-up and wish to continue TDF/FTC on Step 5.

[1] If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

[4] The only required chemistry test is creatinine. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

[5] Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase. If testing was performed within the last month prior to Day 0, testing may be deferred at the discretion of the site investigator.

[7] Adherence counseling is not conducted during a participant's final visit of Step 5

[8] Refer to instructions in the interviewer-administered and CASI assessments as well as the Schedule of Forms for whom and when these assessments should be administered.

Revisions 5 a-e **Section F. Addendum To The Main Sample Informed Consent Form**

Only the impacted paragraphs and table sections from Appendix V, Section F are depicted.

5a. From participant choices listed in Addendum to the Main Sample Informed Consent Form:

You have been told which medication you are on. We are now able to offer you the following choices if you wish to continue in the next part of the study:

- Stay on CAB if you are already on it
- Stay on TDF/FTC if you are already on it
- Switch to getting CAB if you are on TDF/FTC and it is safe for you to do so
- Switch from CAB to TDF/FTC
- Receive CAB if you are on the annual visit schedule now and it is deemed safe for you to start CAB again or to start it for the first time
- **If you are HIV infected and you have been coming to this clinic already for a visit every 3 months, you will complete the remainder of these visits in this next part of the study.**

5b. Under "**New Steps of the Study"**

IF YOU CHOOSE TO STAY ON TDF/FTC OR START TDF/FTC:

Step 5: If you have been getting TDF/FTC pills and you choose to continue, or if you have been on CAB and choose to start TDF/FTC, you will come to the clinic for visits every 3 months for 3 years from the time that you enrolled in the study**, or for one year since your last injection of CAB, whichever is longer**. We will tell you when your ~~3 years~~ **time** in the study will end.

5c. Under **"Steps and Procedures"**

No matter which new step you start in, we will review the information in this consent form with you and answer any questions you may have. We will discuss which study product you would like to choose and ask you questions about your decision. The new steps also include the procedures listed at each visit marked with an X in Steps 4a, 4b, 4c, and 5 below.

There may be special circumstances where your time in this part of the study may be different (shorter or longer) from what is outlined in this consent form to ensure your safety. We will tell you if this happens and how long you will be followed.

5d. Under **"Steps and Procedures"**

STEP 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections - if you choose to continue CAB injections

Procedures	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Discuss with you any challenges of attending your injection visits and getting shots	X	X	X	X	X	X	~~X~~

5e. Under **"Steps and Procedures"**

STEP 5: Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC - If you choose to stay on or switch to TDF/FTC, or after you complete Step 4c

Procedures	Day 0	Weeks 12, 36 (60, 84, 108, 132, if required)	Week 24, 48 (72, 96, 120, 144, if required)
Discuss with you any challenges of taking a pill every day (except at your final visit)	X	X	X