HIV Prevention Trials Network

Letter of Amendment # 2 to:

HPTN 084-01

HPTN 084-01: Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Females – A Sub-study of HPTN 084

DAIDS Study ID: 38655

Version 1.0, dated 14 October 2019

Date of Letter of Amendment: 20 August 2021

LETTER OF AMENDMENT 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.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Signature of Investigator of Record	Date (DD MM YYYY)

Name of Investigator of Record
(printed)

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The following information impacts the HPTN 084-01 study and must be forwarded to all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs before implementation.

The information contained in this LoA does impact the informed consent forms (ICFs).

Upon receiving final IRB/EC approval for this LoA, sites should implement the LoA immediately. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). As part of the registration package, sites must submit the Letter of Amendment Investigatory Signature Page, signed and dated by the Investigator of Record. Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with the LoA and any IRB correspondence should be retained in the site's regulatory files.

If the full HPTN 084-01 protocol is amended in the future, the changes in this LoA will be incorporated into the next version.

Summary of Revisions and Rationale

1. **Revision 1:** The team protocol roster has been edited.
2. **Revisions 2, 4, 5, 9, and 15:** Target participant sample size for this study is now changed from 50 to 55 participants.
3. **Revisions 2, 6, and 14:** Clarification is made so that sites may use generic TDF/FTC and do not necessarily need to dispense brand name Truvada®, in the case(s) wherein a participant does not wish to join the HPTN 084 Open Label Extension (OLE) in Step 3, once available. Relatedly, a footnote is added to Appendix II to indicate that the TDF/FTC is only provided to a participant if they do not choose to remain on injections in Step 3.
4. **Revision 3:** Change is made in the CAB LA section to clarify that a participant may choose the HPTN 084 OLE in Step 3. Other text additions regarding participants joining a locally available OLE study have previously been made in LoA #1.
5. **Revisions 7 and 11:** Text has been edited to convey the retirement of the DAIDS Critical Event (CE) Policy and to further define an Investigator's responsibilities in lieu of the CE Policy.

6. **Revision 8, 10, 16, and 17:** Qualitative sample size change is made regarding qualitative analysis, so that the study may interview up to 15 participants and up to 15 parents (up to 15 total, across the 3 sites).
7. **Revision 12:** Details around the use of the DAIDS SCORE (Site Clinical Operations and Research Essentials) Manual have been added.
8. **Revision 13:** Details have been added regarding remote monitoring in this study and a related reference has been added to the References Section (Section 11).
9. **Revision 14:** HIV testing has been added to all safety visits in Step 2, to be in line with the parent protocol (HPTN 084) and to identify any potential HIV diagnoses in participants in a more timely manner.

Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Changes below have occurred with this LoA (LoA #2). Any additional changes were previously made with LoA #1.

Revision 1: Protocol Team Roster

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Revision 2: SCHEMA

SCHEMA

Study Size:
Approximately 5~~0~~**5**.

Study Duration:
Participant recruitment will take approximately 12 months. Oral study product will be administered for 5 weeks, followed by 29 weeks on injectable product then quarterly visits for 48 weeks after final injection. All participants who have received at least one injection will be followed for 48 weeks after their last injection. Waning levels of cabotegravir (the PK tail) will be covered with locally sourced oral **Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®; generic may be used)** ~~TENOFOVIR/EMTRICITABINE (TRADE NAMETrade name: TDF/FTC, TRUVADA®)~~ for daily use for 48 weeks. Total study duration per participant will be approximately 21 months.

Study Regimen:
Step 1 – oral cabotegravir (30mg tablet); Step 2 – injectable cabotegravir 3 mL (600 mg) intramuscular (IM) injection; Step 3 – Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®; **generic may be used**) ~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)~~ (300mg/200mg tablet)

Revision 3: Section 1.5.2 CAB LA

1.5.2 CAB LA

During the 76-week follow-up phase of the HPTN 077 study[39], differences were observed in the median time to undetectable cabotegravir levels between men and women: 42.7 weeks (range 20.4-134) in men as compared to 66.3 weeks (range 17.7-182) in women. CAB was detected in plasma in 22% of men and 63% of women at 60 weeks and 13% of men and 44% of women at 76 weeks post the last injection). The observed pharmacokinetics in HPTN 077 supported the development of CAB for HIV prevention using 600mg IM every 8 weeks with a 4-week loading dose for all sexes.[40] Although the medium waning PK tail for women participating in HTPN 077 was 66.3 weeks, the HPTN 084-01 team has determined that participants in this trial should receive **Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®)**~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)~~ for 48 weeks **or they should join the HPTN 084 OLE (open label extension) study**~~, in order to mimic the parent trial, HPTN 084~~.

Revision 4: Section 2.3 Study Design and Overview

2.3 Study Design and Overview

We propose a single arm, open label, safety, tolerability, and acceptability study (n=5~~0~~**5**) in sexually-active, healthy adolescents assigned female sex at birth.

Revision 5: Section 3.0 Study Population

3.0 STUDY POPULATION

Approximately 5~~0~~**5** participants will be included in this study. Each site will be asked to work with its Community Advisory Board and outreach, education and recruitment teams to develop a recruitment plan appropriate for the local population. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. Study participants will be recruited as described in Section 3.3. Requirements related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively. Individual sites will be given enrollment targets such that overall cross-site enrollment meets overall protocol goals.

Revision 6: Section 4.1.1 Oral Product

4.1.1 Oral Product

Step 3 – **Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®; generic may be used)** ~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)~~ is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF) in each tablet. The tablets must be stored as per the manufacturer's recommendation. Refer to the package insert for recommended storage conditions.

Revision 7: Section 6.6 Critical Events Reporting

6.6 Critical Events Reporting

~~Per the DAIDS policy on Identification and Classification of Critical Events, a critical event is defined as an unanticipated study-related incident that is likely to cause harm or increase the risk of harm to participants or others or has a significant adverse impact on study outcomes or integrity. All such events must be reported following procedures specified in the DAIDS Critical Events Manual, available at: https://www.niaid.nih.gov/sites/default/files/criticaleventsmanual.pdf.~~

Revision 8: Section 7.1 Review of Study Design

7.1 Review of Study Design

The sample size for this study will be set to enroll approximately 5~~0~~**5** participants. The sample size for this protocol (n=5~~0~~**5**) is the number of participants agreed upon by the industry sponsor and regulators in order to provide supplementary safety and behavioral data on adolescents in collaboration with the HPTN 083 and HPTN 084 adult trials. The primary aims of the study are focused on safety, tolerability, and acceptability of this long-acting product.

Finally, in-depth qualitative interviews will be conducted with ~~10~~**up to 15 participants (**total**,** across all sites**)** after Week 34 to explore issues of acceptability and preference for oral tablets and/or injections. Additionally, up to **15**~~10~~ parents/guardians of participants (total, across all sites) will be asked to participate in in-depth interviews to explore facilitators and barriers to adolescent enrollment in biomedical clinical trials.

Revision 9: Section 7.3 Sample Size

7.3 Sample Size

The sample size for this protocol (n=5**5**~~0~~) is the number of participants agreed upon by the industry sponsor and regulators in order to provide supplementary safety and behavioral data on adolescents in collaboration with the HPTN 083 and HPTN 084 adult trials. The goal of the safety evaluation for this study is to identify safety concerns associated with CAB LA.

Since each of the primary endpoints is a proportion, Table 1. Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 5**5**~~0~~. shows the precision (confidence interval width) that will be obtained for each endpoint with a sample size of 5**5**~~0~~.

Table 1. Width of 95% confidence interval for estimated proportion as a function of the true proportion, assuming a sample size of 5**5**~~0~~.

True proportion	Width of 95% CI
0.1	± 0.0**79**~~83~~
0.2	± 0.1**0**~~1~~
0.3	± 0.1**2**~~3~~
0.4	± 0.1**3**~~4~~
0.5	± 0.1**3**~~4~~

The study will recruit participants to ensure that at least 5**5**~~0~~ participants progress to the injection phase.

Revision 10: Section 7.4.7 Acceptability

7.4.7 Acceptability

A subset of **up to 15**~~10~~ **(total, across sites)** willing participants will complete an in-depth interview (IDI) to be scheduled after the Week 34 visit. In addition, up to ~~10~~**15 (total, across sites)** parents of participants will be invited to participate in in-depth interviews that will explore facilitators and barriers to adolescent participation in biomedical HIV prevention trials. When conducting a qualitative exploration, the sampling method should be designed to include a range of possible perspectives on the phenomenon under study, thus ideal qualitative samples are purposive in nature. For this study, we will utilize a purposive sampling strategy, which will allow for consideration of the concepts of range, saturation/redundancy, and stratification in the sampling frame. We will ask sites to identify potential participants as well as parents/caregivers who would be interested in and comfortable with sharing their experiences with the study product as well as study procedures. Data on acceptability and factors affecting adherence will be collected during the IDI, including questions that explore the use and the acceptability of both the oral and injectable CAB, along with examination of preference for pills or injections. Additional interview topics will include challenges to study participation as well as product use. We will also discuss with participants the acceptability of parental involvement in the consent process.

Revision 11: Section 8.1 Ethical Review

8.1 Ethical Review

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 are responsible for the submission of continuing review to the DAIDS Protocol Registration Office (PRO), in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

Revision 12: Section 8.2 Informed Consent

8.2 Informed Consent

Participants will document their provision of informed consent and assent 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.

Revision 13: Section 10.4 Study Monitoring

10.4 Study Monitoring

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.[50] 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~~S~~ite investigators will **also** allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC; NIAID and/or its contractors; site IRBs/ECs; other local or international regulatory authorities (including the OHRP and US FDA); or, if appropriate, ViiV. A site visit log will be maintained at each study site to document all visits.

11.0 REFERENCES

50. 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

Revision 14: Section 12.2 Appendix II

12.2 APPENDIX II. SCHEDULE OF EVALUATIONS – INJECTION PHASE (Step 2)

WEEKS in Study (shaded column = injection visit)	**Wk 5**	**Wk 6**	**Wk 9**	**Wk 10**	**Wk 17**	**Wk 18**	**Wk 25**	**Wk 26**	**Wk 33**	**Wk 34**
ADMINISTRATIVE, BEHAVIORAL, REGULATORY										
Locator information	X	X	X	X	X	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X	X	X	X	X	X
Condoms per local SOC	X	X	X	X	X	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)	X		X		X		X		X	
Qualitative interviews begin (approximately)										X
CLINICAL EVALUATIONS & PROCEDURES										
Adherence, HIV prevention/risk reduction counselling	X	X	X	X	X	X	X	X	X	X
Contraception counselling and provision or verification of use	X		X		X		X		X	
Medical history[1], concomitant medications, targeted physical exam	X	X	X	X	X	X	X	X	X	X
Hep B vaccination (if needed) [2]		X							X	
Blood collection	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X	X	X	X	X	X	X	X	X
Injections for all participants	X		X		X		X		X	
ISR evaluation		X		X		X		X		X
Provision of **Tenofovir/emtricitabine (Trade name: TDF/FTC, Truvada®; generic may be used)** ~~TENOFOVIR/EMTRICITABINE (TRADE NAME: TDF/FTC, TRUVADA®)~~ provision (3 months' worth) [3]										X
LOCAL LABORATORY EVALUATIONS & PROCEDURES										
HIV testing~~[3]~~**[4]**	X	**X**	X	**X**	X	**X**	X	**X**	X	**X**
Pregnancy testing~~[4]~~**[5]**	X		X		X		X		X	
CBC with differential	X	X	X	X	X	X	X	X	X	X
Chemistry testing~~[5]~~**[6]**	X	X	X	X	X	X	X	X	X	X
Liver function testing~~[6]~~**[7]**	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile~~[7]~~**[8]**	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	X
Syphilis testing									X	
GC/CT testing (urine or vaginal swab)					X				X	
Urinalysis (protein, glucose)	X	X	X	X	X	X	X	X	X	X
Plasma storage~~[8]~~**[9]**	X	X	X	X	X	X	X	X	X	X

[3] Provision of TDF/FTC does not happen at Week 34 if the participant chooses to remain on injections.

** The numbers for footnotes 4 through 9 have also been changed to accommodate the new footnote number (3). Any other changes made within the footnotes for this appendix (Appendix II) are covered under LoA #1 (3 Dec 2020).

Revision 15: Appendix VII (Sample Informed Consent)

In this study, we want to know if it is safe and acceptable for adolescent women who do not have HIV to take an anti-HIV drug called cabotegravir (CAB). We would also like to look at the tolerability, or side effects, of CAB. CAB is a new drug that is still being studied and is not yet approved by the FDA, or U.S. Food and Drug Administration. Other studies showed that CAB can treat people who have HIV infection and it has recently been shown to prevent HIV infection. Another way to prevent HIV is to use condoms and/or take the PrEP pill called Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada®) every day. But some people have a hard time remembering to take a pill every day, so it is a good idea to have other HIV prevention options. With CAB, people would get injections every 8 weeks and would not have to remember to take a pill every day. It is important that we learn what happens when adolescents use CAB for HIV prevention and whether it is safe and acceptable.

You are being invited to join this study because you live in sub-Saharan Africa, where young women are at high risk of getting infected with HIV – as many as five to ten out of 100 each year. This study will be offered to about 55 women under 18 years old across several study sites in Africa. The person in charge of the study at [insert site name] is [insert name of IoR]. The United States National Institutes of Health is paying for the study.

Some of the questions that we want to answer with this study are:
- **Is it safe for adolescent women to take CAB pills and CAB injections?**
- **Is it acceptable and practical for adolescent women to use CAB for HIV prevention?**
- **Are adolescent women able to make it to the clinic for injection appointments?**
- **What do parents/guardians think about their daughters using CAB for HIV prevention?**

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

Revision 16: Appendix IX (Sample Informed Consent for Adolescent Interview)

Appendix IX: SAMPLE INFORMED CONSENT FOR ADOLESCENT INTERVIEWS with PARENT/GUARDIAN PERMISSION

Entering the sub-study
In order to understand better what makes it easier or harder for young women in this study to get CAB injections as directed, we will be doing interviews with up to 1**5**~~0~~ young women at participating sites. You have been selected to take part in one interview sometime after your last CAB injection.

Revision 17: Appendix X (Sample Informed Consent for Parent/Guardian Interview)

Appendix X: PARENT/GUARDIAN IN-DEPTH INTERVIEW INFORMED CONSENT FORM

Entering the sub-study
We will be doing interviews with up to 1**5**~~0~~ parents/guardians at participating sites (total, across sites). You have been selected to take part in one interview sometime after your child's last CAB injection.