Letter of Amendment #2 to:

HPTN 084: A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women

Version 5.0, 06 October 2023

DAIDS Document ID: 38070
IND # 122,744

LoA #2: FINAL of 25 April 2024

Instructions to the Study Sites from the Sponsor

The following information impacts the HPTN 084 study and must be forwarded to all responsible Institutional Review Boards (IRBs)/Ethics Committees (ECs) and any other required regulatory authorities as soon as possible for their information, review and approval. This Letter of Amendment (LOA) must be approved all required regulatory authorities before implementation.

The following information may also impact the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this letter of amendment.

The HPTN 084 protocol will be fully amended in the future and will include the modifications outlined in this LOA.

Text appearing below in highlighted **bold** will be added, and text appearing in highlighted ~~strike-through~~ will be deleted.

Summary of Revisions and Rationale

An additional two "safety net" injections are being added to Step 6 of the HPTN 084, V5.0 protocol. These two "safety net" injections ensure access to CAB LA for all participants willing and eligible to continue using CAB LA until it is available via other means. Any additional injections beyond these 4 (Week 128 of the Open Label Extension) would need CMC and Sponsor approval on an individual case-by-case basis.

Implementation

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit an 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. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. Please file this LoA, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential document files for HPTN 084.

Protocol Signature Page

HPTN 084

A Phase 3 Double Blind Safety and Efficacy Study of Long-Acting Injectable Cabotegravir Compared to Daily Oral TDF/FTC for Pre-Exposure Prophylaxis in HIV-Uninfected Women DAIDS Document ID # 38070

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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

Protocol Sections Revised:

1. Appendix VIII: Procedures for Offering Open Label (OL) Cabotegravir- The Next Part of HPTN 084 Background, Purpose and Overview, Description of Steps

   2.0 Purpose and Overview

   <u>OL2 of the Study</u>

   OL2 of the study was introduced with the version 4.0 amendment. The v5.0 amendment extends CAB LA to participants on Step 6 for up to two additional injection cycles (i.e., approximately 16 weeks), as is appropriate, and updates risk language. **LOA#2, to the v5.0 protocol adds up to two more injection cycles (approximately 16 weeks) to the Step 6 SOE.**

   2.1 Duration

   NOTE: Under the **LOA#2 to** v5.0 amendment, participants on maintenance doses of CAB LA at **Week 96 of Step 6 ~~their last visit~~** who wish to continue taking CAB LA but whose local access to CAB LA is delayed for any reason will be offered up to **four** ~~two~~ additional doses. If these participants ~~elect to~~ receive **four** ~~two~~ additional CAB LA doses, then their time in the study will be extended by approximately **32** ~~16~~ more weeks. **After Week 96, participants are to be transitioned off of HPTN 084 as soon as CAB LA is available locally.**

   3 Description of Steps 4, 5 and 6 during the V5.0 Protocol

   * NOTE: Participants who reach Week 96 on maintenance doses of CAB LA and wish to continue using CAB LA but where local access is delayed for any reason will be offered up to **four** ~~two~~ additional doses (approximately **32** ~~16~~ weeks) on Step 6. These participants will have visits at Weeks 104, ~~and~~ 112, **120 and 128 if needed to maintain therapeutic levels of CAB LA. After Week 96, participants are to be transitioned off of HPTN 084 as soon as CAB LA is available locally.**

   3.1 Overview of Steps 4~~d~~, 5 and 6

   <u>Step 4d</u>

   Step 4d is for participants who are pregnant and who have had at least one CAB LA injection ever. All participants interested in participating in Step 4d will be asked to provide informed consent for this Step prior to any study activities. Step 4d does not apply to participants who have never received a CAB LA injection.

   NOTE: Any participants who become pregnant after week 96 of Step 6 may be offered participation in Step 4d. However, those participants will only be required to complete the Step 4d SOE through to pregnancy outcome or delivery, whichever comes first. These participants will not be required to complete the Step 4d post-partum visit schedule apart from completion of week 48 post-partum assessments which can be done in person or remotely in order to provide information on infant health. If CAB LA access if available locally, participants may be transitioned to local CAB LA services after delivery. Where CAB LA is not available locally, participants may continue to receive CAB LA injections per the Step 4d post-partum schedule until local CAB LA access is available. Sites should consult the CMC to confirm their management plans for these participants.

Step 6

* NOTE: Participants who reach Week 96 on maintenance doses of CAB LA and wish to continue using CAB LA but where CAB LA local access is delayed will be offered **up to four** ~~two~~ additional doses (approximately **32** ~~16~~ weeks) on Step 6. These participants will have visits at Weeks 104, ~~and~~ 112**, 120 and 128 if needed to maintain therapeutic levels of CAB LA. After Week 96, participants are to be transitioned off of HPTN 084 as soon as CAB LA is available locally.**

2. Schedule of Evaluations (Appendix VIII)

Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants who were Exposed to CAB LA, and Their Infants**&**
Footnote added:

& Any participants who become pregnant after week 96 of Step 6 may be offered participation in Step 4d. However, those participants will only be required to complete the Step 4d SOE through to pregnancy outcome or delivery, whichever comes first. These participants will not be required to complete the Step 4d post-partum visit schedule apart from completion of week 48 post-partum assessments which can be done in person or remotely in order to provide information on infant health. If CAB LA access if available locally, participants may be transitioned to local CAB LA services after delivery.
Where CAB LA is not available locally, participants may continue to receive CAB LA injections per the Step 4d post-partum schedule until local CAB LA access is available. Sites should consult the CMC to confirm their management plans for these participants.

Appendix VIII: Schedule of Evaluations for Step 6-Procedures for Participants on Maintenance Doses of CAB LA weeks 49-96 (or Weeks 49 **up to Week 128** ~~112~~)

Time in Step 6	Week 56	Week 64	Week 72	Week 80	Week 88	Week 96[#]	Week 104[&]	Week 112	**Weeks 120 and 128[@]**
ADMINISTRATIVE PROCEDURES									
Informed Consent	X						X[$]		
Locator information	X	X	X	X	X	X	X	X	**X**
Acceptability assessment			X			X		X	
Behavioral assessment			X			X	X	X	
HIV prevention counseling	X	X	X	X	X	X	X	X	**X**
Offer condoms per local SOC	X	X	X	X	X	X	X	X	**X**
CLINICAL EVALUATIONS & PROCEDURES									
Medical history, concomitant medications, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X	X	X	X	X	X	X	X	**X**
Blood collection	X	X	X	X	X	X	X	X	**X**
Urine collection[1]	X	X	X	X	X	X	X	X	**X**

Time in Step 6	Week 56	Week 64	Week 72	Week 80	Week 88	Week 96[#]	Week 104[&]	Week 112	**Weeks 120 and 128[@]**
Vaginal swab collection[2]			X			X		X	
Adherence counseling[3]	X	X	X	X	X	X	X	X	**X**
Administer CAB LA	X	X	X	X	X	X	X	X	**X**
LOCAL LABORATORY EVALUATIONS & PROCEDURES									
HIV testing[4]	X	X	X	X	X	X	X	X	**X**
HIV viral load testing[5]	X	X	X	X	X	X	X	X	**X**
Pregnancy testing, only if indicated[1]	X	X	X	X	X	X	X	X	**X**
Chemistry testing[9]						X		X	
Liver function testing[6]						X		X	
Syphilis testing			X			X		X	
GC/CT and TV testing[2]			X			X		X	
Plasma storage[7,8]	X	X	X	X	X	X	X	X	**X**
DBS storage[8]	X	X	X	X	X	X	X	X	**X**

At Week 96, site staff must determine whether the PPT can access CAB LA locally, outside of the trial. If the PPT has access to CAB LA, Week 96 will be the final visit. If local access to CAB LA is delayed for any reason, offer the PPT ~~up to two~~ additional injections on the study. **Participants will only receive injections until CAB LA is locally available. Some participants may need to receive two injections until CAB LA is available; other participants may receive three and a minority may require all four safety net injections. Participants must be transitioned off of HPTN 084 after Week 96 as soon as possible. "Safety net" injections are available for** Weeks 104~~, and~~ 112, **120 and 128.**

[$] At Week 104 of Step 6, if a PPT has not already been reconsented for Week 104, ~~and~~ 112**, 120 and 128** visits, she must be consented.

[@] NOTE: HPTN 084 intends to transition participants off of the trial as soon as possible after the Week 96 study visit. However, should CAB LA not be available locally to participants at the Week 128 injection visit, the site will reach out to the CMC for guidance. A member of the CMC will consult with the sponsor and additional injections may be approved on a per participant basis. If additional injections are granted the site will follow the same procedures outlined in the Step 6 SOE for visits at Weeks 120/128.

[&] Any participants who become pregnant after week 96 of Step 6 may be offered participation in Step 4d. However, those participants will only be required to complete the Step 4d SOE through to pregnancy outcome or delivery, whichever comes first. These participants will not be required to complete the Step 4d post-partum visit schedule apart from completion of week 48 post-partum assessments which can be done in person or remotely in order to provide information on infant health.
If CAB LA access if available locally, participants may be transitioned to local CAB LA services after delivery. However, where CAB LA is not available locally, participants may continue to receive CAB LA injections per the Step 4d post-partum schedule until local CAB LA access is available. Sites should consult the CMC to confirm their management plans for these participants.

3. Addendum To The Main Sample Informed Consent Form

Why is the research study being updated?
The team is updating the research study to make two changes. Those changes are highlighted in grey so that you can easily see them in this document. The first change is to add new CAB LA side effects. Those side effects are explained later in this document and the team at your study site will talk with you about them. The second change being made is to add **four** ~~two~~ more CAB LA injections at the end of the second open label period for any participants who cannot yet access CAB LA locally.

What happens next?

Now, let's talk about what is happening next and what is new to the study. In brief, all study visits and their timing will stay the same. Most study visits will be spaced eight weeks apart (every other month).
We will collect the same types of samples and do the same types of testing. The only change is that **four** ~~two~~ additional CAB LA injection visits will be added to the end of the second open-label period for participants who need them. We hoped that at the end of the second open-label period CAB LA would be locally available to any study participant who wanted to take it. The company that makes CAB LA is actively working with all 20 HPTN 084 study sites to do that. Just in case it takes a bit longer than expected the study team is adding the option of providing **four** ~~two~~ additional CAB LA injections at the end of the second open label period. Only participants who need those **four** ~~two~~ injections will receive them.

<u>WHAT HAPPENS DURING THE SECOND OPEN LABEL PERIOD</u>

Once you reach the clinic visit at Week 96, if you are not pregnant, the study staff will talk to you about whether you wish to continue taking CAB LA after the study. If you want to keep taking it, it will be available from the company that makes CAB LA locally. Just in case it takes a bit longer than anticipated for CAB LA to available, we are adding up to **four**~~two~~ additional injection appointments to the end of the study. **These injection visits occur at Weeks 104, 112, 120 and 128.** Only participants who need those extra injections will receive them.

For women receiving the extra injections, we will:

- Confirm where you live and how to contact you.
- **At Weeks 104, 112, 120 and 128 we will a**~~A~~sk you questions. We will ask about your sexual behavior, how your health is, whether you have experienced any side effects from taking study medication, whether you have taken any other medicines, and whether you have used alcohol or drugs. We will also ask how you feel about getting injections at Week 112.

What happens if you become pregnant during the study?

If you become pregnant after Open Label Study Week 96, you may still be eligible to get CAB LA injections via the Pregnancy and Infant sub-study up until delivery or termination of pregnancy. During this time, we will evaluate your health as well as the health of your fetus.

If CAB LA is available locally to you via other means than HPTN 084, you will no longer be eligible for CAB LA injections and your study participation will end. We will however wish to contact you either in person or via other means to assess your health and your infant's health 48 weeks after delivery.

If CAB LA is not available locally to you via other means than HPTN 084, you have the option to continue in HPTN 084 through 48 weeks post-partum in the pregnancy substudy with regular evaluations as listed below.