

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 3.0, 12 August 2021

DAIDS Document ID: 38070

IND # 122, 744

FINAL LoA #2: 03 February 2022

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

1. [Revision 1](#): Capitalized the “L” and “C” of Laboratory Center in the List of Abbreviations and Acronyms.
2. [Revision 2](#): Added clarifying language to Appendix VIII, Section 2 “Purpose and Overview.”
3. [Revision 3](#): Updated/corrected the duration of participant follow up in Appendix VIII, Section 2.1 “Duration.”
4. [Revision 4](#): Added several clarifications to Appendix VIII, Section 3 “Description of Steps 4 and 5” and the SOEs.
5. [Revision 5](#): Removed erroneous text from the Schedule of Evaluations for “Appendix VIII: Schedule of Evaluations for Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first.”
6. [Revision 6](#): Corrections/Typographical errors to the Schedule of Evaluations for “Appendix VIII: Schedule of Evaluations for Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC” as well as to footnotes of the table were made.
7. [Revision 7](#): Revisions to text related to Step 4d: Clarification to sampling for infants during the Pregnancy and Infant Sub-Study were made. Typographical errors were also corrected.
8. [Revision 8](#): Added clarifying text to the section “Schedule of Additional Procedures for Women with Reactive/ Positive HIV Tests”
9. [Revision 9](#): Corrected typographical error within Appendix VIII, Section A. “Information in the Main Protocol that is Not Relevant to Protocol, Version 3.0,” Section 7.0 (Modified from the main Protocol).”
10. [Revision 10](#): Corrected guidance for participants with Grade 3 ALTs within Appendix VIII, “Guidance on Toxicity Management for Specified Toxicities.”

11. [Revision 11](#): Corrected guidance for participants with CPK elevations within Appendix VIII, “Guidance on Toxicity Management for Specified Toxicities.”
12. [Revision 12](#): Added some clarifying text and corrected some typographical errors within Appendix VIII, the following changes were made to the “Addendum To The Main Sample Informed Consent Form.”

Implementation

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. 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

Version 3.0, 12 August 2021

Letter of Amendment # 2, dated 3 February 2022, FINAL v1.0

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

1. **Revision 1:** Capitalized the “L” and “C” of Laboratory Center in the List of Abbreviations and Acronyms

LC (HPTN) Laboratory Center

2. **Revision 2:** Added clarifications in Appendix VIII, Section 2 “Purpose and Overview.”

Revision 2, Change 1

“Participants will be offered the opportunity to either take OL CAB LA 600 mg IM every eight weeks (with the exception of participants who previously discontinued CAB LA for confirmed safety reasons) or to take OL daily TDF/FTC. Participants switching from TDF/FTC or re-starting CAB LA may choose to start CAB LA immediately or they may start at a later time point but no later than 24 weeks after they begin the OL portion of the study, **with the exception of pregnant women. Pregnant women who took CAB LA prior to pregnancy but switched to TDF/FTC may elect to re-start CAB LA up to 24 weeks post-delivery with permission from the CMC.**

Participants may also choose to discontinue study products, (e.g., if they have reduced HIV risk); participants discontinuing study products will be asked to continue in follow-up for 48 weeks off of study product (**according to Step 4c, but withholding product**). Below are two images illustrating the options participants will have during the open-label portion of the study.

Revision 2, Change 2

This Appendix includes procedures for new Steps, Step 4 (OL CAB LA or OL TDF/FTC) and Step 5 (OL TDF/FTC following premature discontinuation of CAB LA), the respective visit schedule for each participant group, updated toxicity management instructions, an updated sample ICF, and other relevant information from the original protocol that pertains to study procedures for Steps 4 and 5. Please note, this section also contains an SOE for following pregnant and breastfeeding participants **who have been exposed to CAB LA.**

3. **Revision 3:** Updated the duration of participant follow up in Appendix VIII, Section 2.1 “Duration.”

Revision 3, Change 1

Only a minority of participants will be followed for up to ~~400~~ **103** weeks (those who discontinue CAB LA prematurely during the OL component and are offered 48 weeks of TDF/FTC to cover the pharmacokinetic (PK) “tail” **who also elect a four-week OLI and a four-week loading dose and stop Step 4c at Week 47**).

Pregnant participants may be enrolled in the study for up to ~~148~~ **160** weeks (four-week OLI optional, **plus 4 four-week loading dose**, plus 48 weeks OL CAB LA **on Step 4c, plus first 8 weeks of Step 5** (and only if pregnancy occurs within 8 weeks of last injection) plus 96 weeks of follow-up through pregnancy and post-partum period with final assessment of infant outcome at 48 weeks post-partum.

4. **Revision 4:** Added several clarifications in Appendix VIII, Section 3 “Description of Steps 4 and 5” and the SOEs.

Revision 4, Change 1)

All participants will be offered OL CAB LA, except for those participants who discontinued **study product (either TDF/FTC or CAB LA)** for safety reasons earlier in the study. Participants who permanently discontinued study products during the blinded portion of the study due to HIV infection, HBV infection or for a study product-related AE that would deem the continuation or initiation of CAB unsafe are NOT eligible to restart or begin CAB. The CMC may be contacted for questions related to

study product AEs of concern for participants interested in continuing or initiating CAB and whether it is safe to do so.

Revision 4, Change 2)

~~All~~ **The majority** of participants **on version 2.0** will be followed for at least 48 weeks in Step 4 (unless they decline consent for further participation). Step 5 will be offered to all participants who receive at least one injection of CAB LA in Step 4 but who prematurely discontinue CAB LA in Step 4. In Step 5 participants will be followed for 48 weeks on OL TDF/FTC to cover the CAB LA tail. Details of Steps 4 and 5 are included below.

Revision 4, Change 3)

Added “and Their Infants” to item 4)

The following Steps will be followed during the OL evaluation:

- 1) Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first
- 2) Step 4b- Procedures for Participants Initiating or Re-starting CAB LA without the Optional Oral Lead-in; the Initial Dose Visit
- 3) Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC
- 4) Step 4d- Procedures for Pregnant/Breastfeeding Participants **and Their Infants**

Revision 4, Change 4)

Step 4

During Step 4c, all participants will be followed for 48 weeks, irrespective of OL study product choice (CAB LA or TDF/FTC), at visits every eight weeks for a total of ~~six~~ **seven** visits.

Revision 4, Change 5)

Step 4d is for participants who become pregnant in Step 4 and first 8 weeks of Step 5, who have had at least one CAB LA injection ever. **Infants born to mothers participating in Step 4d are also eligible for sub-study activities.** ~~This s~~ **Step 4d** does not apply to participants who have never received a CAB LA injection.

Revision 4, Change 6)

At the first pregnancy test positive visit, participants will have their pregnancy confirmed on a second independent sample. Participants should be counselled about the risks and benefits of continuing CAB through pregnancy and breastfeeding, and offered an opportunity to re-consent to receive CAB LA injections during pregnancy. **Participants also will have the option to provide or decline consent for sub-study infant assessment.** Participants who need more time to consider their decision can have their CAB LA injection temporarily deferred, within the remaining visit window. Participants who decline ~~to~~ ~~continue~~ CAB LA during pregnancy and breastfeeding, **and who have never been exposed to CAB LA,** will be offered OL TDF/FTC **and followed on Step 4c.** All pregnant participants who have had at least one CAB LA injection will be followed up in accordance with the pregnancy schedule of evaluations in Step 4d. CAB LA injections will be administered every eight weeks in those that consent; **those that do not will be offered OL TDF/FTC.** Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.

At delivery, **where feasible**, a maternal blood sample and cord blood sample will be collected from the mother, and where feasible an infant blood sample will be collected **at delivery.** ~~(week 0)~~ During the post-partum period, blood and breastmilk samples will be collected from the mother, and blood samples **will be collected** from the **infant per the** (see Step 4d SOE). Infant outcomes will be assessed at delivery up to approximately 12 months later (Week 48 of Step 4d).

Revision 4, Change 7)

Step 5

Only participants who received OL CAB LA in Step 4 **and** who discontinue CAB LA early **during Step 4** for safety or other reasons will have the option to transition to Step 5.

- Revision 5: Revisions to text related to Step 4a:** Removed erroneous text from the Schedule of Evaluations for “Appendix VIII: Schedule of Evaluations for Step 4a- Procedures for Participants Initially Randomized to TDF/FTC Who Elect to Move to OL CAB LA with Optional Oral Lead-in first.”

Revision 5, Change 1)

	DAY 0/ of Step 4a
ADMINISTRATIVE, BEHAVIORAL, REGULATORY	
Informed consent	X
Locator information	X
Offer CAB LA and counseling on direct to inject vs. oral lead in	X
Acceptability assessment	X
Behavioral assessment	X
HIV prevention counseling	X
Offer condoms	X
CLINICAL EVALUATIONS & PROCEDURES	
Medical history, con meds, targeted physical exam (with pulse, BP, weight and BMI calculated at each visit)	X
Blood collection	X
Urine collection ¹	X
For those who select oral lead in: Dispense study product (enough for 4 weeks)	X
Adherence counseling ²	X
LOCAL LABORATORY EVALUATIONS & PROCEDURES	
HIV testing ³	X
HIV viral load testing ⁴	X
Pregnancy testing ¹	X
CBC with differential, if not done in Step 4a	X
Chemistry testing ⁵	X
Liver function tests ⁶	X
Fasting lipid profile, if not done in Step 4a ⁷	X
Plasma storage ^{8,9}	X
DBS storage ⁹	X

6. **Revision 6: Revisions to text related to Step 4c:** A correction to the Schedule of Evaluations for “Appendix VIII: Schedule of Evaluations for Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC” was made. Moved footnote #6 to the visit it applies to; did not belong to the whole row. In addition, made several typographical corrections to the footnotes.

Revision 6, Change 1)

Chemistry testing, if not done in Step 4a or 4b ⁶	X ⁶					X				X
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Revision 6, Change 2)

~~** for those that have not already re-consented as part of step 4 a or b~~

** for those that have not already re-consented as part of step 4 a or b

1 Pregnancy testing may be performed in the clinic or the laboratory. Results must be available the same day as sample collection and before product is administered. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the participant is still pregnant. If a participant has a positive pregnancy test, **and is eligible**, follow her according to Step 4d.

2 GC/CT and TV testing to be done only if not performed in the past 3 months. GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed ~~9~~ using a vaginal swab. If a woman is menstruating, the swab may be collected at a later visit and all testing using the swab may be performed at that later visit.

4 The HIV testing algorithm is provided in the SSP Manual. HIV rapid ~~testing~~ testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

7. **Revision 7: Revisions to text related to Step 4d:** Clarification to sampling for infants during the Pregnancy and Infant Sub-Study were made.

Revision 7, Change 1)

The following additional Local Laboratory tests and procedures are required for Step 4d.

- **Infant HIV testing**
- **Cord blood storage**
- **Breast milk storage**
- **Infant plasma storage**
- **Infant DBS storage**

Procedures for sample processing, testing and storage are provided in the SSP Manual. Assessments using stored samples from the Pregnancy and Infant Sub-Study will not be returned to study sites or participants.

Revision 7, Change 2)

Text “and Their Infants” was added to the title of the Schedule of Evaluations for “Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants **and Their Infants**”

Time on Pregnancy and Infant Sub-study	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Delivery	Week 2, pp	Week 4, pp	Week 8, pp	Week 16 pp	Week 24, pp	Week 32, pp	Week 40, pp	Week 48, pp	
Cord blood collection ¹⁸												X									
Infant blood collection ¹⁸												X	X	X	X	X	X	X	X	X	X
Infant HIV testing, if the mother has one or more reactive/positive HIV test results is confirmed to have HIV infection ¹³												X	X	X	X	X	X	X	X	X	X
Cord blood storage ^{9,14}												X									
Dried blood spot storage ^{9,17}												X	X	X	X	X	X	X	X	X	X
Infant plasma storage ^{9,14}												X	X	X	X	X	X	X	X	X	X

⁸ Stored plasma may be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9).

¹³ **Perform infant HIV testing at this visit and all subsequent study visits using local infant testing algorithms if the mother has one or more reactive/positive tests, even if HIV infection in the mother is not confirmed.** If HIV testing indicates that an infant has HIV infection, a second confirmatory visit should be conducted to confirm HIV infection in the infant. If infant infection is confirmed, resistance testing should be performed locally using a separate (additional) infant sample collected for this purpose.

¹⁴ **Stored cord blood and plasma samples will be used for PK analysis and may be used for other assessments, including virology testing. Results from this testing will not be returned to the study sites or participants.**

¹⁷ **Stored DBS samples may be used for retrospective HIV testing and other assessments; DBS will be prepared in the processing laboratory and will not be collected via heel stick. Results from this testing will not be returned to the study site or participants.**

¹⁸ **Cord blood and infant blood should be collected if feasible. If blood collection is not possible, simply note that in participant files.**

8. Revision 8: Added text to the section “Schedule of Additional Procedures for Women with Reactive/Positive HIV Tests”

Participants with a confirmed HIV infection must be linked to care as soon as possible (care is not provided by the study) and subsequently, the IOR must confirm that the participant has achieved viral suppression on antiretroviral treatment. **(The IOR must attempt to confirm viral suppression either until the end of the study, or until documentation of viral suppression is obtained.)** The participant’s ART regimen must be documented as concomitant medication. Once viral suppression is confirmed, the participant will be terminated from the study.

9. Revision 9: Within Appendix VIII, Section A. “Information in the Main Protocol that is Not Relevant to Protocol, Version 3.0,” Section 7.0 (Modified from the main Protocol)

Participants will be censored from the OL Cab efficacy and safety analyses using an ~~On-Blinded-Study-Product (OBSP)~~ approach i.e. at the end of study participation or 10 weeks after the date of last Cab injection (6 weeks, if only one injection has been given), whichever comes first.

Also, changed abbreviation OBSP to OSP throughout this section.

10. Revision 10: Within Appendix VIII, “Guidance on Toxicity Management for Specified Toxicities,” the following text was revised.

Guidance on Toxicity Management for Specified Toxicities:

ALT

Grade 3 and higher	<p><u>Injectable CAB (Step 4c):</u> For Grade 3 and higher ALT, study product will be permanently discontinued. Repeat testing should be performed as soon as possible, and participants should be followed every two weeks until levels are \leq Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up, or in rare cases where alternative etiology has been identified and ALT has resolved to Grade 1 or lower, restart of study product.</p> <p>Participants who are permanently discontinued from study product will be transitioned to Step 5 local clinical care for clinical management and local prevention services and terminated from the study per CMC direction.</p> <p><u>TDF/FTC (Step 4c): Contact the CMC for management instruction.</u></p> <p><u>Open label TDF/FTC (Step 5):</u> Participants will be followed per the Schedule of Procedures and Evaluations for Step 5; for participants who have transitioned to Step 5 from Step 4c, the decision whether it is safe to provide oral TDF/FTC will be made with guidance from the CMC. When Step 5 concludes in these cases, the participant will be referred to local prevention services. Note that Step 5 concludes at Week 48 for all participants transitioning from Step 4c.</p>
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11. Revision 11: Within Appendix VIII, “Guidance on Toxicity Management for Specified Toxicities,” the following text was removed.

Guidance on Toxicity Management for Specified Toxicities:

Creatine Phosphokinase (CPK)

Note the following for cases of exercise-induced CPK abnormalities:

Note the following for cases of exercise-induced CPK abnormalities: Cases of CPK abnormality \geq Grade 3 or higher, presumed to be exercise induced, accompanied by $<$ Grade 3 ALT must be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grades 3 and 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product ~~and the participant will be followed annually for HIV testing only until the conclusion of Step 2 of the study.~~ All such cases must be reported to the CMC.

12. Revision 12: Within Appendix VIII, the following changes were made to the “Addendum To The Main Sample Informed Consent Form”

Revision 12, Change 1)

At Weeks 2, 4, 8, 16 and 24 we collect **5mLs** (1 teaspoon) of breastmilk to learn about levels of CAB in breastmilk.

Revision 12, Change 2)

-We would like to collect a small amount of blood from your baby at Weeks 2, 4, 8, 16, 24, **32, 40** and 48.

At the end of 48 weeks your participation in the study will end. At that time, if you want to keep taking CAB LA you can choose to move to locally provided CAB LA that is not part of the study. The company making CAB LA is working to offer it to study participants after this research study ends. If you prefer, we can refer you to a local HIV prevention program.

*** Please note that if any test results suggest that you may have an HIV infection, we will also test your baby for an HIV at every study visit to determine if the baby has an HIV infection, even if we can't determine your HIV status at that time. We will refer both you and your baby to a local HIV care clinic for treatment if HIV infection is confirmed, or if your results indicate that you may have an unconfirmed infection.**

Revision 12, Change 3)

What happens if you become infected with HIV during this part of the study?

If you become infected with HIV during this next part of the study, you will be immediately referred for local care and treatment of HIV. We will not provide care for HIV infection as part of this study.

We will ask you to come back to the study clinic for a few appointments. At the first visit, we will confirm your contact information, we will offer you condoms, provide HIV counseling, do a physical exam and collect blood. Some blood will be stored, if you agree to that. The rest of the blood will be used to help us better understand how the infection occurred and how the early course of infection may be impacted by the study drug you were taking. This includes testing for HIV resistance. **This testing will be performed for research use only. The results will not be returned to the study site or to you. Separate testing will be performed at the study site for your clinical care.** If you get infected with HIV while on CAB, **or if your HIV test results indicate that you may be infected,** you might need to take medications that are not like CAB to treat the HIV infection. We will also want to make sure that the amount of HIV virus in your blood is responding well to treatment. Once we have confirmed that your HIV is responding well to treatment, your participation in the study will end.

Revision 12, Change 4)

Removed “and” in one option in the samples for future testing options for minors who participated in HPTN 084-01

_____ I do not agree to have samples of my blood stored ~~and~~ long-term for future testing.

Revision 12, Change 5)

Added “long-term” in these two options for participants in the pregnancy infant sub-study

_____ I agree to let the team store umbilical cord blood, blood from my baby and breastmilk samples **long-term** for future research.

_____ I do not agree to let the team store umbilical cord blood, blood from my baby and breastmilk samples **long-term** for future research.