

Letter of Amendment #1 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 #1: FINAL of 01 December 2023

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: Throughout the protocol, typographical errors were corrected. The word ‘Draft’ was corrected to ‘Final’ in several places, including the Protocol Signature Page and the Informed Consent Forms.
2. Revision 2: Removed cholesterol from Step 6 footnote #6. No cholesterol testing is being done during Step 6 of the V5 protocol.
3. Revision 3: In Section 6.3 (Safety Monitoring) an inconsistent sentence was removed. Sites are now instructed to contact both CMC and HIV aliases. Neither participants nor study staff re blinded to product choice.
4. Revision 4: In Sections 9.2 and 9.2.2 removed an old note; after the DSMB review a years ago the trial was unblinded.
5. Revision 5: The US Food and Drug Administration (FDA) requested clarification of text in Section 9.2.2 of the v5.0 protocol. The phrase “subset of samples” led to confusion. This LOA clarifies that CAB PK will be evaluated for the subset of **participants** who consent to the sub-study and subsequent sample collection, according to Appendix VIII Schedule of Evaluations for Step 4d.
6. Revision 6: In the section ‘Guidance on Toxicity Management for Specified Toxicities’, removed one sentence that was outdated and related to Step 2 which is irrelevant to the v5.0 protocol.
7. Revision 7: Throughout the Addendum to the Main Sample Informed Consent Form, updated study procedures to be aligned with the Step 4d, Step 5, and Step 6 SOEs. No changes were made to the SOEs. The text in the consents now aligns with the respective SOEs.

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
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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

- Revision 1: Throughout protocol made corrections to typos. Changed the word ‘draft’ to ‘final’ in several places including to the Protocol Signature Page and the informed consents forms.
- Revision 2: Removed erroneous mention of “cholesterol” from Step 6 footnote #6. No fasting lipid panel or cholesterol testing is being done during Step 6 of the V5 protocol.

⁶ AST, ALT, total bilirubin, ~~cholesterol~~.

- Revision 3: In Section 6.3 (Safety Monitoring). Removed inconsistent sentence. Sites were instructed to contact both CMC and HIV aliases once the unblinded portion of the trial ended.

Section 6.3 (Safety Monitoring)

A sub-group of the Protocol Team, including the Protocol Chair, DAIDS Medical Officer, and other site investigators will serve as members of the CMC. The CMC provides support to sites regarding individual participant clinical management (e.g., questions related to eligibility, toxicity management, clinical holds of study drug, etc.). ~~Sites will be instructed to not solicit guidance from the CMC regarding HIV seroconversions in order to ensure to the extent possible that the team is blinded to the number of infections occurring in the study.~~ The HPTN LC will be available for questions regarding HIV confirmation testing.

- Revision 4: In sections 9.2 (Stored Specimens) and 9.2.2 (Pharmacology), removed this “NOTE” since participants are no longer blinded.

Section 9.2 (Stored Specimens)

Plasma, whole blood, cord blood, breast milk and DBS will be stored at the local site throughout the study. A subset of the stored samples will be shipped to the HPTN LC (located in the US) for Quality Assurance (QA) and other assessments. As indicated below, testing on stored samples will be performed by the HPTN LC or another laboratory designated by the HPTN LC.

~~NOTE: Samples may be unblinded at the HPTN Laboratory Center (Pharmacology Laboratory only), so the relevant assays are only performed on participants who received CAB LA. In any such case, no one outside the Pharmacology Laboratory will be unblinded prior to the end of the trial (see Section 5.18).~~

Section 9.2.2 (Pharmacology)

Revision 3, Change 2, Section 9.2.2 (Pharmacology)

~~NOTE: Samples may be unblinded at the HPTN Laboratory Center (Pharmacology Laboratory only) for the adherence subset testing so the relevant assays are only performed on participants who received CAB LA. The HPTN LC (Pharmacology Laboratory) will not be unblinded for remaining analysis until the end of Step 2.~~

- Revision 5: In section 9.2.2 (Pharmacology), edits to this paragraph were made in response to a comment from FDA about this text: ‘subset of samples.’ Edits now clarify that CAB PK will be evaluated for the subset of participants who consented to the sub-study and subsequent sample collection, according to Appendix VIII- Scheule of Evaluations for Step 4d.

Plasma, cord blood, **and** breast milk ~~and DBS~~ samples for drug concentrations will be collected throughout the study from all participants **who consent to the pregnancy sub-study and subsequent sample collection.** ~~although PK testing~~ **Pharmacokinetic testing will be limited to a subset of participants who consent to the sub-study and subsequent sample collection.**

Additional details will be outlined in the pregnancy and infant sub-study statistical analysis plan the samples. Plasma and DBS samples will be processed and frozen locally for subsequent shipment to the HPTN LC following procedures outlined in the SSP Manual. Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Results will not be returned to the study participants.

Revision 6: In the section ‘Guidance on Toxicity Management for Specified Toxicities’, a sentence was deleted because it is outdated; Step 2 is not part of the v5.0 protocol.

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

Revision 7: Addendum to the Main Sample Informed Consent Form

Throughout the Addendum to the Main Sample Informed Consent Form, updated study procedures to be aligned with the Step 4d, Step 5, and Step 6 SOEs. No changes were made to the SOEs. The text in the consents now aligns with the respective SOEs.