

FINAL Letter of Amendment # 2 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 1.0, February 2, 2016

DAIDS Document ID: 20725

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Final Version of LoA # 2: 26 July 2016

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study, including the study informed consent forms, 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 and all required approvals of **both** protocol Version 1.0 and this LoA must be obtained before initiating this study. Likewise, all participants must provide written informed consent for this study using site-specific informed consent forms that correspond to this LoA.

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. This notification must be received prior to implementation of this LoA. Receipt of this notification, as well as an initial registration notification for protocol Version 1.0 and LoA # 1, will be confirmed as part of the site-specific study activation process for this study.

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: The protocol team roster is updated as follows: Kailazarid Gomez-Feliciano has been added as a senior study manager at the HPTN Leadership and Operations Center at FHI 360; the contact information for Sheldon Fields has been updated as he is no longer at Charles Drew University of Medicine and Science; Bijal Patel has replaced Michelle Wildman as the Division of AIDS (DAIDS) protocol pharmacist on the study, as Michelle Wildman is no longer employed at DAIDS; and the contact information for Tim Holtz has been updated as he is no longer stationed in Thailand.

Revision 2: The background section is updated to include a case of ALT elevation from HPTN 077, which is included in the current Investigator’s Brochure (Version 5.0, dated January 6, 2016). Elevations had previously only been seen in HIV-infected participants, and this case occurred in an HIV-uninfected participant. The language is modified to this effect, but intentionally removes absolute counts of cases, in anticipation that additional cases may occur.

Revision 3: Letter of Amendment (LOA) # 1, dated May 24, 2016, modified the language regarding the exclusion criterion for buttock implants. Further modifications have been made to remove specific types of implants and to add fillers, in order to be more inclusive with regard to the type of buttock augmentations that are exclusionary. Instructions are also added to contact the Clinical Management Committee (CMC) regarding specific cases or questions. The criterion as written in this LoA # 2 supercedes the criterion as written in LoA # 1.

Revision 4: Two paragraphs in Appendix III – Toxicity Management – are updated to remove reference to a section that does not exist and to remove reference to specific toxicity management guidelines for AST. This language appears in the Phase 2a safety study of cabotegravir (HPTN 077), and does not apply to this study.

Revision 5 a – c: The sample informed consent form in Appendix IV has been updated as follows:

- 5a corrects the length of time someone may be in Step 2 of the study, as stated under the “Study Groups” section of the sample informed consent. The correction of this error was inadvertently omitted from LoA # 1, dated May 24, 2016, which corrected two of the three occurrences of this error in the same section.
- 5b adds language regarding the DXA subset stating that results of the scans will be provided to participants at the end of the study.
- 5c modifies language per Revision 2 above.

IMPLEMENTATION

Revision 1 | Protocol Team Roster

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Revision 2 Section 1.5 Hepatic and Central Nervous System Adverse Events

Note: The first paragraph of this section is impacted by this change and is depicted below.

As part of the early phase development of cabotegravir (**Phase 2a HPTN 077**, Phase 2b LATTE and LATTE-2), some participants ~~with HIV infection and pre-existing liver disease~~ developed transaminase elevations, which were clinically asymptomatic and resolved rapidly with cessation of study product.

Revision 3 Section 3.2: Exclusion Criteria

Note: Only the exclusion criterion that is impacted by this change is depicted below.

Change included in LoA #1, May 24, 2016:

- Surgically-placed **or injected silicone/industrial product** buttock implants, per self-report

Updated for LoA # 2 (and takes precedence over LoA #1):

- Surgically-placed or injected ~~silicone/industrial product~~ buttock implants **or fillers**, per self-report. **Contact the CMC for guidance regarding questions about individual cases.**

Revision 4 Appendix III: Toxicity Management

Note: Only the two paragraphs impacted by this change are depicted below, and are the second and third paragraphs to appear at the beginning of the Toxicity Management section.

The following general guidance refers to all AEs except for ~~AST/ALT~~. Refer ~~to the section below~~ **“Specific Guidance on Transitioning from Oral to Injectable Phase”**, as well as to the table below for specific guidance for ALT.

Grade 1 or 2

In general, participants who develop a Grade 1 or 2 AE regardless of relatedness to study product, and that is not specifically addressed in the Table below may continue use of the study product per protocol. **See an exception to this under “Specific Guidance on Transitioning from Oral to Injectable Phase”.**

Revision 5a Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: Only the relevant section included under the “STUDY GROUPS” section of the sample consent form is impacted by this change and is depicted below.

In Step 1, everyone starts the study by taking pills for 5 weeks. This is to see if you have any serious side effects to the study drugs before you starting getting the shots.

In Step 2, everyone takes pills and gets shots. This step will last up to **four three** and a half years, depending on when you started in the study.

In Step 3, everyone gets the real TDF/FTC every day for about a year, then your participation in the study will end and we will refer you to local HIV prevention services. There are no current plans for the study to offer the injectable CAB drug to study participants after the completion of the study.

Revision 5b Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: The last bullet under “STUDY PROCEDURES, Screening Visit”, is impacted by this change and depicted below.

- **[Sites participating in the DXA substudy to include this:]** We may ask you to be a part of a group that gets a bone mineral density-energy x-ray absorptimetry (DXA) scan. A DXA scan is a special kind of x-ray using a small amount of radiation, allowing the doctor to see parts of the body better than a regular x-ray. The scan will be done at the Enrollment visit (this visit), and 2 other times during the study (Weeks 57 and 105). **The results of the DXA scans will be given to you at the end of the study.**

Revision 5c Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: The second paragraph under “RISKS AND/OR DISCOMFORTS, Study Medications, The side effects of cabotegravir include:” is impacted by this change and depicted below.

There have been some people who were taking this medicine **in other studies** who have had liver side effects. **Most Some** of these people were HIV-infected (HIV positive) and **they all had had** damage to their liver before taking the CAB study medication. **In those studies, w**While taking the study medication, their blood tests showed that their liver was irritated, although they felt well. The medications were stopped, and the liver blood tests **are returned to** normal. In this study, anyone with HIV-infection, Hepatitis C (or B), or any liver irritation will not be allowed to be in the study.