

## 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**

**Protocol Version 1.0, dated 2 March 2017**

**DAIDS Document ID: 38070**

**IND #: 122,744**

**Final Letter of Amendment Version: 24 January 2018**

---

#### Summary of Revisions and Rationale

1. The protocol has been updated to adopt the FDA suggestion of unblinding participants who become pregnant.
2. The protocol now clearly indicates that sites must be selected to participate in sub-studies.
3. Memory aids have been removed from the protocol in response to site feedback.
4. Typographical errors have been corrected.
5. Additional regulatory agencies have been added to the consent form at the request of DAIDS.

---

#### Implementation

The information contained in this Letter of Amendment (LoA) impacts the HPTN 084 study, including the study informed consent form, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for 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. Note that required approvals of protocol Version 1.0, LoA #1 and LoA #2 must be obtained before initiating this study.

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.

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 084.

If the HPTN 084 protocol is fully amended in the future, this LoA 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.

**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**  
**FINAL, Version 1.0, dated 2 March 2017**  
**DAIDS Document ID: 38070**

**A Study of the HIV Prevention Trials Network (HPTN)**

**Letter of Amendment #2, Dated: 24 January 2018**

**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 (MM/DD/YYYY)**

\_\_\_\_\_  
**Name of Investigator of Record (print name)**

---

**Revision 1-Related Changes: Protocol Updates in Response to FDA Request**

---

**Revision 1, Change 1)** Wording has been added to Section 5.14, Pregnancy

“Confirmed Pregnancies

**Participants with a positive pregnancy test will require confirmation of pregnancy at a subsequent visit at least four weeks later.** All pregnancies that occur during the course of the study must be reported to the CMC within seven days of site awareness (either upon confirmation by urine or blood pregnancy testing during a study visit or as reported by the participant between study visits). Site staff will refer to their SOP for detailed management.

All pregnant participants **with a confirmed positive pregnancy test (four weeks after the initial pregnancy test)** will be **unblinded and** followed by the study every 12 weeks. Regardless of the randomization assignment or point in the study, all pregnant participants will be placed on open-label TDF/FTC for the duration of the pregnancy. No participant with a **recognized positive pregnancy test** will be administered CAB, CAB LA, or CAB LA placebo. The site IoR or designee will refer pregnant participants to all applicable pregnancy-related services **and will be provided a letter to obstetric services detailing participation in the trial**; however, sites will not be responsible for paying for pregnancy-related care. The site IoR or designee will counsel any participants who become pregnant regarding possible risks to the fetus according to site-specific SOPs.

Once pregnancy outcome is reached, if the participant is not breastfeeding, she may resume study product and visits according to the SOE. Should a participant who delivers a child during the study elect to breastfeed, she will stay on open-label TDF/FTC and will be followed per the SOE. Once a participant has finished breastfeeding, she may resume study product and visits according to the SOE. **To most closely reflect eventual real-world practice, unblinded participants will have the option to return to open-label study product in their original randomization arm (either injectable cabotegravir or oral TDF/FTC).** Participants who are pregnant at their last study visit will continue to be followed until the pregnancy outcome is ascertained or it is determined that the pregnancy outcome cannot be ascertained through all reasonable means. All pregnancy outcomes will be reported on relevant CRFs. Outcomes meeting criteria for expedited AE (EAE) reporting also will be reported. **Infants will be followed up for one year post-partum to ascertain final pregnancy outcomes in respect to congenital anomalies.”**

**Revision 1, Change 2)** Wording has been added to Section 5.17, Planned Unblinding of Study Participants

“When the required number of incident HIV endpoints has been reached, or when the last participant completes scheduled Step 2 follow-up (meaning all participants have moved to Step 3), and when all corresponding procedures at the HPTN SDMC, LC, and LOC have been completed, including final confirmation from the HPTN SDMC, the study will be unblinded.

**Participants with a confirmed pregnancy (see section 5.14) will be unblinded. Procedures for unblinding pregnant participants will be detailed in the SSP.”**

**Revision 1, Change 3)** Wording has been added to Section 7.6, Blinding

**“ In addition, as described in sections 5.14 and 5.17, participants with a confirmed pregnancy will be unblinded. Participants who are unblinded due to pregnancy may restart open-label study product in their original randomization arm (open label CAB LA or TDF/FTC) following delivery and cessation of breastfeeding.”**

**Revision 1, Change 4)** Wording has been added to Section 7.8.1, Analyses of Primary Efficacy Objective

- “To evaluate the relative efficacy of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2)

**Person** To preserve the integrity of randomization, **person**-time and HIV events will be included in this analysis based on each individual’s scheduled duration of participation in steps 1 and 2, as determined at randomization. Specifically, individuals who refuse injections, pills or both, or ~~need to~~ **who** receive open-label **TDF/FTC study product** (e.g. due to pregnancy) will be included in this analysis in their original randomization arm for the duration of their originally scheduled participation in Steps 1 and 2.

The Hazard Ratio (HR) comparing CAB LA vs TDF/FTC and a 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment arm as the only covariate, stratified by site using data from steps 1 and 2 only. We will test the hypothesis  $H_0: HR = 1.0$  versus  $H_a: HR \neq 1.0$  using  $\alpha = 0.05$ . Treatment efficacy will be estimated as  $TE = 1 - HR$ .

**Revision 1, Change 5)** Wording in the Consent Form, Pregnancy Section has been added

“If you become pregnant during the study, we will refer you for obstetric care. We will stop giving you injections, ~~although we will not know which study products you were assigned to,~~ **we will tell you and your doctor which study group you were assigned to** and switch you to open-label TDF/FTC. Your study schedule will be reduced and we will only ask you to come to clinic one time every 12 weeks during your pregnancy. **During these study visits, we will collect blood and urine samples and at some visits we will also collect vaginal swabs. We will perform some, but not all, of the same study lab tests you agreed to.** Although you will stop injections, if you were receiving CAB it is likely that the levels of CAB will last in your body and the baby’s body throughout your pregnancy up until delivery. If you are still pregnant after your last visit, we will ask you or your doctor to provide updates on the progress of your pregnancy and its outcome **for the first year of the baby’s life**. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.”

**Revision 2-Related Changes: Text was Updated to Indicate Sites Must be Selected for Sub-studies**

**Revision 2, Change 1)** Text has been added to Section 2.5.1, Participating Sites/Institutions

“Participating sites are listed in the SSP Manual, and are located in SSA.

**Sub-studies for HPTN 084 will not necessarily be conducted at all sites. Sites selected for sub-studies will be notified in writing by the study Chairs.”**

### Revision 3-Related Changes: Removed the Memory Aid from the Protocol

#### Revision 3, Change 1) Updated Appendix Ib: Schedule of Evaluations- Step 2, Injection Phase

WEEKS in Study (shaded column = injection/ dispense pills visit)	5	6	9	13	17	21	25	33	41	42	49	57	65	73	81	89	97	105	113	121	129	137	145	153	161	169	177	185	
CLINICAL EVALUATIONS & PROCEDURES																													
Dispense-ISR-Memory-Aid	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review-ISR-Memory-Aid		X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ISR evaluation		X	X	X					X																				

#### Revision 3, Change 2) Updated Appendix Ic: Schedule of Evaluations- Step 3, Follow-up Phase

Time in Step 3	Step 3, Day 0*	Step 3, Week 12	Step 3, Week 24	Step 3, Week 36	Step 3, Week 48
CLINICAL EVALUATIONS & PROCEDURES					
Dispense pills to all participants	X	X	X	X	
Adherence counseling for all participants	X	X	X	X	
Review-ISR-Memory Aid	X				

#### Revision 3, Change 3) Removed text relating to the Memory Aid from the Consent Form, Step 2: Week 5 Visit Activities

“This visit will last up X hours. During this visit, in addition to the activities described above for all Step 2 visits, the study staff will:

- Ask you to answer questions about your sexual behavior.
- Staff will give you more pills. Staff will also count your leftover pills and talk with you about ways to help you take your pills. If it seems to you or to the study staff that you are having challenges, we will try to help by working through these with you.
- The first shot will be given in your buttock. ~~Staff will also give you a memory aid that you can record any side effects from the shots on. You will bring the memory aid back with you at the next visit to review with staff.”~~

#### Revision 3, Change 4) Removed text relating to the Memory Aid from the Consent Form, Step 2: CAB LA Injection of TDF/FTC Dispensing Visit Activities

- “A shot will be given in your buttock. Shots will be given approximately every 2 months (8 weeks) after the first two are given. ~~Staff will also give you a memory aid that you can record any side effects from the shots on. You will bring the memory aid back with you at the next visit to review with staff.”~~

**Revision 3, Change 5)** Removed text relating to the Memory Aid from the Consent Form, Step 3: Follow-up Visits

- ~~“Review the memory aid with staff (on Day 0 only).”~~

**Revision 4-Related Changes: Corrected Typographical Errors Throughout the Protocol**

**Revision 4, Change 1)** Corrected Error in Section 5.11.2: After Study Enrollment/Randomization

“Step 3

Participants with confirmed HIV infection during Step 3 will have their TDF/FTC stopped and be followed quarterly at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by **guidance from the HIV alias the CMC**. Study product will be discontinued and participants will be referred for care.”

**Revision 4, Change 2)** Corrected Error in Section 6.2.2: Reporting Requirements for This Study

“The SAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

- In addition to SAEs, sites will report in an expedited manner the following results ~~(must be both in order to require expedited reporting)~~:
- ALT  $\geq$  3xULN AND total bilirubin  $\geq$  2xULN **(must be both in order to require expedited reporting)**
- Any seizure event”

**Revision 4, Change 3)** Corrected Error in Section 7.2.3 Title, Secondary Endpoints

- “7.2.3 Secondary ~~Efficiency~~ Endpoints”

**Revision 4, Change 4)** Corrected Error in Section 7.2.4: Tertiary Endpoints

**“7.2.4 Tertiary Endpoints**

- Sexual risk (number of partners, number of unprotected sex acts)
- Incident STIs (GC/CT, trichomonas, syphilis ~~adjudicated~~)
- Grade 2 or higher clinical and laboratory adverse events (AEs) broken down by BMI  $\leq/\geq$  25kg/m<sup>2</sup>”

**Revision 4, Change 5)** Corrected Error in Section 7.6: Blinding

~~“In addition, as noted in Section 5.11.2, an Investigator can request unblinding to the HPTN SDMC in the event that a participant becomes infected with HIV during the study, and the SDMC will assist in directly providing the participant’s provider of choice the randomized arm assignment information per their SOP; the randomized assignment will not be provided to the site where the participant was enrolled and followed.”~~

**Revision 4, Change 6)** Corrected Error in wording describing ClinicalTrials.gov in the General Overview of the Consent Form

“Before you decide whether to join the study, we will explain the purpose of the study, the risks and benefits, and what is expected of you. This form includes all of that information in the later pages. ~~A description of this study will also be available on~~ ~~www.ClinicalTrials.gov. The web site will not include information that can identify you and you may look at the web site at any time. After the study ends and the results have been reviewed by the study team, the web site will include a results summary. A~~ description of this study will be available on [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by US law. 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 4, Change 7)** Updated wording in the Pregnancy section of the Consent Form at the request of ProPEP

“If you become pregnant during this study we will ask you to stop the injections. For some people CAB LA could remain in the body for a year or more after the last injection. Because we do not know how long CAB LA may stay in your body and because we do not know what effect CAB may have on a baby during pregnancy, ~~you may wish to~~ **we recommend you** delay becoming pregnant after your last injection, for at least 52 weeks.

During the study, you will receive counseling about your options for preventing pregnancy. You can receive some forms of contraception from the study clinic or be referred to an appropriate clinic for contraception.

- If you change your mind after enrolling in the study and do wish to become pregnant prior to Week 5, you will be terminated from the study.
- If change your mind and desire to become pregnant at any time point after Week 5, we will stop giving you injections as we don’t know how CAB LA might impact a baby. You will be started on open-label oral TDF/FTC (**“open-label” means you will know you are receiving TDF/FTC**) and followed at the regularly scheduled study visits until either the end of your planned Step 2 schedule, or for 48 weeks after beginning TDF/FTC, whichever is later.”

## **Revision 5-Related Changes: Additional Regulatory Agencies Have Been Added to the Consent**

**Revision 5, Change 1)** Added Text to the Confidentiality Section of the Consent Form

### **“CONFIDENTIALITY**

Efforts will be made to keep your study records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. However, your records may be reviewed, under guidelines of the United States Federal Privacy Act, by the United States Food and Drug Administration (FDA); the sponsor of the study (United States National Institutes of Health [NIH]), **other U.S., local, and international regulatory entities may also review study records, as well as** the *[insert name of site]* Institutional Review Board (IRB), Ethic Committee (EC) study staff, study monitors, the companies that make the drugs used in this study, and *(insert applicable local authorities]*.

The study staff will also use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by *[site name]* and studies conducted by other researchers that study staff know about.

Your records may be reviewed by:

- US FDA
- US NIH
- US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- **other U.S., local, and international regulatory entities**
- *[insert names of applicable IRBs/ECs/other local review bodies as applicable]*
- Study staff
- Study monitors
- Companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.)”