

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**

Protocol Version 1.0, dated 2 March 2017

DAIDS Document ID: 38070

IND #: 122,744

Letter of Amendment 1 Version: 15 August 2017

Summary of Revisions and Rationale

1. The Protocol Signature Page text has been updated to match the new template text.
2. A protocol signature page has been added for LoA 1.
3. Risks have been added to the informed consent form to match updated ViiV Healthcare risks for studies using cabotegravir.

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 and LoA # 1 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 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.

Revision 1-Related Changes: Revised Protocol Signature Page to Match Updated Template

Revision 1, Change 1) In accordance with updated template verbiage, the below text has been removed from the Protocol Signature Page, page 14

~~“I agree to maintain all study documentation for at least two years following the date of marketing approval for the study product for the indication in which it was studied, unless otherwise specified by DAIDS, or the HPTN Leadership and Operations Center (LOC) or if other applicable laws, regulations, policies, or other requirements (e.g., State, country specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the US Food and Drug Administration (FDA) is notified that the Investigational New Drug (IND) is discontinued, or if other applicable laws, regulations, policies, or other requirements (e.g., State, country specific, and local laws, and sponsor or institutional policies) exist, the most stringent retention period will be followed.~~

~~Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted to the HPTN Manuscript Review Committee (MRC), and DAIDS for review prior to submission.~~

~~Truvada® is an approved registered drug in the USA and used as one of the study products in protocol HPTN 084. I have read and understand the information in the Truvada® package insert (PI) and the Cabotegravir Investigator Brochure (IB), including the potential risks and side effects of the products under investigation, 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.”~~

Revision 1, Change 2) In accordance with updated template verbiage, the below text has been added to the Protocol Signature Page, pages 14 and 15

“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.”

Revision 2- A protocol signature page has been added for LoA 1

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 Study ID # 38070

**Version 1.0, 2 March 2017, Letter of Amendment #1
Dated August 15, 2017**

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

**Name of Investigator of Record
(printed)**

Revision 3-Related Changes: Informed Consent Risks have been Updated

Revision 3, Change 1) Additional potential side effects of the study product, long-acting cabotegravir, have been added to the consent form, page 119

“The side effects of CAB include:

Headaches, diarrhea, and fatigue. With the CAB that you get as an injection, people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising where they got the injection. Other reported side effects include muscle aches, irritated nasal passages, runny nose, sore throat, upper respiratory tract infection, difficulty sleeping, abnormal dreams/nightmares, depression, increase in the level of enzymes in the muscle (creatinine phosphokinase), nausea, vomiting (being sick), flatulence (gas or wind), fever and dizziness.”

Revision 3, Change 2) Additional wording which has been agreed upon by the FDA and ViiV regarding animal study data during pregnancy has been added to the consent form, page 122

We would like you to be cautious about falling pregnant. There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. Birth defects have not been observed in animal studies with CAB, to date. In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug. That is why if you are female and participating in this study, you cannot be pregnant, and we want you to take birth control the entire time you are in the study and also for a year after.

Revision 3, Change 3) Additional information which has been agreed upon by the FDA and ViiV regarding pregnancy has been added to the consent form, page 123

If you become pregnant ~~intentionally~~ 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,** 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. **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. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.