

**FINAL Letter of Amendment # 3 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 2.0, dated 6 November 2019  
DAIDS Document ID: 38070  
IND #: 122,744**

**FINAL Letter of Amendment Version: 22 October 2020**

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All sites should follow applicable government, health authority, and institutional policies with respect to conduct of study visits and procedures, with utmost importance placed on the health and well-being of study participants and study staff. Site investigators should continue to follow current protocol specifications for communication with the Protocol Team and/or Clinical Management Committee and should contact the Clinical Management Committee (084cmc@hptn.org) with any questions or concerns regarding this LoA or management of study participants.

When such a determination is made, study sites will be formally notified and instructed to inform IRBs/ECs and other applicable regulatory entities.

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.

**Summary of Revisions and Rationale**

1. The HPTN 084 Study Monitoring Committee (SMC) has recommended enrollment increase to approximately 3,350 participants.
2. Remote Source Document Verification has been added to the protocol in order to account for instances when on-site monitoring is not possible.
3. Details from Clarification Memo 2 have been added.

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**Implementation**

The information contained in this Letter of Amendment (LoA) impacts the HPTN 084 study 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.

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 document files for HPTN 084.

**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 2.0, dated 6 November 2019**  
**DAIDS Document ID: 38070**

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

**FINAL Letter of Amendment #3, Dated 22 October 2020**

**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)**

# 1. Increase of Enrollment to 3,350 study participants

## SCHEMA

**Study Size:** Approximately ~~3,200~~ **3,350** women will be enrolled.

### 2.5 Study Design and Overview

This is a Phase 3, randomized, multi-site, two-arm, double-blind study of CAB LA compared to daily oral TDF/FTC for HIV prevention. Approximately ~~3,200~~ **3,350** participants will be enrolled and randomized 1:1 to Arm A (CAB LA and placebo TDF/FTC) and Arm B (TDF/FTC and CAB LA placebo) through the three Steps listed below. When the study reaches the required number of incident HIV endpoints (114), all participants will begin open-label daily oral TDF/FTC for approximately 48 weeks (to “cover the tail”), starting no later than 8 weeks after the last injection.

### 3.0 STUDY POPULATION

Approximately ~~3,200~~ **3,350** HIV-uninfected women from SSA will be included in this study. Each site will be asked to work with its Community Advisory Board and outreach, education and recruitment teams to develop a recruitment plan appropriate for the local population. Participants will be selected for the study according to the criteria in Sections 3.1 and 3.2. Study participants will be recruited as described in Section 3.3. Requirements related to participant retention and withdrawal from the study are described in Sections 3.5 and 3.6, respectively. Individual sites will be given enrollment targets such that overall cross-site enrollment meets overall protocol goals.

### 7.4 Accrual and Retention

Approximately ~~3,200~~ **3,350** participants will be enrolled in approximately 24 months and followed through Steps 1 and 2 for 1.6 to 3.6 years and on oral TDF/FTC for an additional 48 weeks. An average annual retention rate of at least 95% percent will be targeted (87 - 88% for the entire Step 1 and 2 follow-up period).

#### 7.8.4.3 Selection of an NI Margin

Table 7.5 gives, for CAB LA adherence of 85% and various levels of TDF/FTC adherence, the NI margin that preserves at least 50% of the active control benefit based on the meta-regression shown in Figure 7.1, as well as the expected RR under the alternative hypothesis, number of events needed for 90% power, and sample size. Other assumptions are as noted previously. Based on this table an analysis with a variable, adherence-dependent margin that preserves at least 50% of the proven benefit of TDF/FTC is well-powered for TDF/FTC adherence from 55% up to 64%, assuming the **original design** sample size of 3200. **Power will be greater for the increased sample size target of 3350.**

## Appendix IV: Sample Screening and Enrollment Informed Consent Form

### GENERAL OVERVIEW

You are being invited to take part in an investigational research study related to the Human Immunodeficiency Virus (HIV) because you live in a part of the world where women have a high risk of becoming infected with the virus. The HIV virus causes Acquired Immunodeficiency Syndrome (AIDS). As many as five to ten women out of 100 in SSA are

newly infected with HIV each year. This study will be offered to about ~~3,200~~ **3,350** other women who live in SSA, are HIV-uninfected, and have sex with men.

## **2. Remote Source Document Verification**

### **10.0 ADMINISTRATIVE PROCEDURES**

#### **10.4 Study Monitoring**

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, government or other local, US, or international regulatory authorities/entities (including the OHRP and US FDA). site IRBs/ECs or if appropriate, the SAHPRA, ViiV/Gilead A site visit log will be maintained at each study site to document all visits.

#### **10.4.1 Remote Study Monitoring**

**Due to ongoing travel restrictions during the COVID-19 pandemic, some sites are unable to accommodate onsite monitoring visits. Remote monitoring visits to date consist of quality review of study data available in the Electronic Data Capture system without verification to corresponding source documents. Review of source documentation is a critical component of ensuring data integrity.**

**Four options listed below will enable the facilitation of remote source document verification, which may vary site by site. All offered are HIPAA and 21 CFR Part 11 compliant.**

**Option #1 - Veeva SiteVault Platform- This platform is available for sites to self-subscribe at no cost from Veeva Systems. There is no software to download and the only requirement is internet access. Sites will upload source documents to this secure platform and assign permissions to monitors to access these data for a limited period of time. For sites that are already using this platform in some capacity, they can add specific DAIDS studies to their existing account. In the event that this platform is being used by another entity within the institution, the site can request access to the platform following their internal procedures. However, sites that are not currently using Veeva SiteVault, can obtain additional information by visiting <https://www.veeva.com/products/sitevault/> or**

sign up to try at sites.veeva.com. Veeva SiteVault may require a signed agreement between the site and Veeva Systems.

**Option #2 - Site Controlled SharePoint or Cloud-Based Portal-Some sites may already have a platform which allows for sharing of participant source documents, which could be extended to allow monitor's access. This option must be 21CRF 11 and HIPAA compliant as applicable.**

**Option #3 – Direct Access to Electronic Medical Records by Monitors- This option may be feasible for sites that use Electronic Medical Records, and whose institutional policy allows for direct access of the site's Electronic Medical Record to monitors for a limited period of time. Please contact your institution's Security Officer for required approvals and any agreements to facilitate remote access to participant source documents.**

**Option #4 - Medidata Rave Imaging Solution- This option does not require additional purchase of software and sign-on is through each site's existing single iMedidata account. Sites will upload source documents to this secure platform and monitor permission and access is assigned by the SDMC. There is ongoing discussion regarding the implementation timeline for MediData Rave Imaging Solutions, and the SDMC will contact sites regarding demonstration of this solution.**

### **3. Details from Clarification Memo 2 have been added**

Appendix IV: Sample Screening and Enrollment Informed Consent Form

#### **PREGNANCY**

We do not know if CAB can cause birth defects in babies. Birth defects have not been found in any animal studies of CAB so far. We have information from a different study conducted in Botswana with dolutegravir (DTG), a medicine that is similar to but not the same as cabotegravir (CAB), the medicine being studied in HPTN 084. In that study, some women living with HIV were taking DTG for treatment of HIV infection around the time of conception. That study, known as the Tsepamo study, collected information on 153,899 deliveries at government hospitals throughout public health facilities Botswana from August 2014 to April 2020 and reported on babies that had birth defects of the spinal cord and brain (neural tube defects). These defects occur early on in the development of the pregnancy.

Overall, among 1683 deliveries in women who became pregnant while they were taking dolutegravir, 5 neural tube defects were found, that is a rate of 3 per 1000 babies born. This is compared to 15 neural tube defects in 14,792 babies born to women taking non-dolutegravir antiretroviral therapy for HIV at the time of conception or one in 1000 babies born.

#### **BENEFITS**

There may be no direct benefit for you if you participate in the study.

TDF/FTC is known to protect people from getting HIV if taken daily as directed. The recent

results from the HPTN 083 study comparing CAB to TDF/FTC conducted in men who have sex with men and transgender women at 43 sites globally showed that participants given daily TDF/FTC pills had about three times the number of HIV infections compared to participants getting long-acting CAB. CAB has not yet been shown to protect against ~~getting HIV~~ HIV infection in cisgender women, which is the reason we are doing this study.