

Letter of Amendment #4 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 2.0, November 6, 2019

DAIDS Document ID: 38070

IND # 122, 744

FINAL LoA #4: 16 November 2020

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. Because important new information learned from a pre-planned efficacy and safety review by an independent Data and Safety Monitoring Board may impact study participants, it is expected that sites will submit the changes to the HPTN 084 study specified in this Letter of Amendment (LoA) for approval as soon as possible upon receipt. The content of the LoA is effective upon obtaining all required approvals.

This Letter of Amendment has appended to it a Participant Letter for all study participants (See Appendix I).

Your site is required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Your site will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A 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.

The HPTN 084 protocol will be fully amended in the near future and will include the modifications outlined in this Letter of Amendment.

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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Version 2.0 dated November 6, 2019

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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

Background and Summary of Modifications:

All modifications included in this Letter of Amendment are based on results of a pre-planned interim efficacy and safety review by the National Institute of Allergy and Infectious Diseases (NIAID) Multinational Data and Safety Monitoring Board (DSMB). On 5 November 2020, the NIAID Multinational DSMB was in agreement that the primary question of whether long-acting cabotegravir prevents HIV infection has been answered in the affirmative and was highly statistically significant. Because of these results, the DSMB recommended that blinded portion of the study be stopped, participants unblinded to their study allocation and that the trial results be made available as soon as possible. The study's sponsor (NIAID) accepted the Board's recommendation. A full protocol amendment will be developed; however, the modifications specified below reflect an interim approach to be employed until that amendment is finalized and approved by the sponsor and the IRBs/ECs/other national and local regulatory authorities.

The immediate modifications are summarized below:

- No further screening or enrollment will occur under Version 2.0 of the protocol, dated November 6, 2019, meaning that the portion of the LoA that outlines the recommendation for an increase to 3,350 participants in LoA #3 is null and void.
- Investigators of Record (IoR) will be provided the randomization assignment for their enrolled participants. Each site IoR will then be responsible for informing participants of her randomization assignment as soon as is feasible following approval of a Participant Letter to be administered at the time of unblinding.
- Upon being informed of randomized study drug assignment, participants still receiving study drug will no longer receive the respective placebo study product and will be offered to continue the active study drug to which they were originally assigned until further notice as follows:
 - Participants in Step 1: If any participants remain in Step 1, contact the HPTN 084 Clinical Management Committee for guidance. (084cmc@hptn.org).
 - Participants in Step 2 assigned to active CAB LA: These participants will be offered to continue active CAB LA on the current Step 2 study visit schedule.
 - Participants in Step 2 assigned to active oral TDF/FTC: These participants will be offered to continue active TDF/FTC on the current Step 2 study visit schedule. These participants will be offered CAB when it becomes available.
 - Participants in Step 3 will continue visits per the current Step 3 visit schedule. Participants who reach the final visit of Step 3 prior to obtaining additional CAB drug supply will transition to annual follow-up and be referred to local HIV prevention services. When CAB supply is obtained, these participants will be contacted and offered CAB.
 - In consultation with the study's Clinical Management Committee (CMC), participants who have already completed or terminated study participation for reasons other than HIV infection, an adverse event assessed as related to study product, or other exclusionary reasons as identified by the CMC, will be offered to re-enroll via the upcoming full amendment of the protocol.
- Upon implementation of LoA #4, participants who choose to continue study follow-up as outlined above will follow the current applicable Step-associated Schedule of Procedures and Evaluations with the exception of pill counts at Weeks 2 and 4 and dispensing blinded product and placebo. Only unblinded products will be dispensed.

Appendix I

Sample HPTN 084 Participant Letter/Information Sheet

PRINCIPAL INVESTIGATOR: [Insert PI Name/Affiliation]

Dear HPTN 084 Participant:

The purpose of this letter is to share with you some important results from the HPTN 084 study that have become available after a recent Data and Safety Monitoring Board (DSMB) meeting on 5 November 2020. The DSMB is an independent group that reviews studies and their results while they are happening to ensure the safety and well-being of the study participants. After reading this letter, if you have any questions about this information, we encourage you to talk to the site staff.

The HPTN 084 Study:

The HPTN 084 study is being done at 20 sites in South Africa, Botswana, Eswatini, Zimbabwe, Malawi, Uganda and Kenya and has enrolled 3,224 participants with [X] at this site.

As you know, the purpose of the study is to try to find out if a new drug called cabotegravir (CAB), is as safe and will work better than TDF/FTC in protecting you from getting HIV. As a reminder, TDF/FTC is approved by the U.S. Food and Drug Administration (FDA) [and insert local country if applicable] for the treatment of HIV and also to prevent people from getting HIV.

All participants in this study were put into one of two groups by chance (like the flip of a coin):

- Group 1: Real CAB drug and TDF/FTC placebo (pill that does not have TDF/FTC)
- Group 2: Real TDF/FTC drug and CAB placebo (injections that do not have CAB)

Results of the DSMB review:

At the DSMB meeting on 5 November 2020, the DSMB found that both CAB and TDF/FTC were very good at preventing new HIV infections. They also found that both CAB and daily TDF/FTC pills were safe and well tolerated. They saw that CAB was much better at preventing HIV than TDF/FTC. Participants given daily TDF/FTC pills had approximately nine times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). The DSMB recommended that the blinded part of the study be stopped, that participants be informed of their study group, and that the results be made public.

The HPTN 084 study will continue. The study team wants you to keep coming to this clinic for follow up visits and procedures. In the near future, the protocol will be amended to allow for slight changes to the study visit requirements depending on which active product you are taking and whether you change from TDF/FTC to CAB. You will be given the information and offered an updated consent form at that time. For now, you will stay in the group that you were put in at the beginning of the study. We will tell you what this group is at your visit today.

[To be inserted for sites with participants on Step 1: If you are in the first part of the study (Step 1) and you are on real CAB, you will finish Step 1 and then you will come to the clinic for your first injection and then four weeks later for another injection, and then every 8 weeks after that. If you are on real TDF/FTC, you will finish Step 1 and then come to the clinic every 8 weeks.]

If you are in part of the study where you are getting injections (Step 2), you will come to the clinic as originally planned which is about every 8 weeks. Participants assigned to real CAB will continue to receive real CAB injections but will no longer receive TDF/FTC placebo pills.

Participants assigned to real TDF/FTC will continue to receive real TDF/FTC pills but will no longer receive CAB placebo injections. If this is the real TDF/FTC group, we want to remind you that TDF/FTC works very well to prevent HIV infection if it is taken as prescribed.

If you are in the group that got real TDF/FTC and you want to get CAB, you will be offered CAB when it is available. The study team is working to get more CAB for participants that want it. The study team will also let you know how long you will stay in the study, the new study visits and study procedures now that we have this new information. Any changes in the study must be approved by a group of people that protect your rights and safety (*insert regulatory authorities and Ethics Committees as appropriate*). This group oversees research at this clinic. We will tell you of any decisions about changes in the study and fully explain any changes to you.

Staying in HPTN 084 is entirely your choice. You may choose to leave the study now or at any time in the future without losing any of the care you get at this [*or name local referral clinic or other required local language*] clinic.

If you have any questions now or later about the information in this letter, you may ask the study staff or contact me directly. We will do our best to answer your questions or concerns.

Your participation in the HPTN 084 study has led to a very important discovery about a new way to prevent HIV infection. Staying in this study will help to increase our knowledge. Thank you for participating in HPTN 084.

Sincerely,

[Insert name and contact information of Investigator of Record]

If you have read this letter, or have had it read and explained to you, and understand the information, please sign your name or make your mark below.

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date