

**Letter of Amendment #1 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 3.0, October 31, 2019**

**DAIDS Document ID: 20725**

**IND # 122, 744**

**Final LoA #1: May 19, 2020**

**Instructions to the Study Sites from the Sponsor**

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The following information impacts the HPTN 083 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 083 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 a 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 083.

The HPTN 083 protocol will be fully amended in the near future and will include the modifications outlined in this Letter of Amendment.

## 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 14 May 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 the trial results be made available as soon as possible. The study's sponsor (NIAID), accepted the Board's recommendation. A full protocol amendment is currently being 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 3.0 of the protocol, dated October 31, 2019.
- Investigators of Record (IoR) will be provided the randomization assignment for their enrolled participants. An "Instructions to Sites" document will be provided to all sites along with this Letter of Amendment which includes an estimated timeframe for when this information will be available. Each site IoR will then be responsible for informing participants of his or her randomization assignment as soon as is feasible.
- All participants will be offered active CAB when it becomes available unless they permanently discontinued CAB due to an adverse event assessed as related to study product. The timeframe for when adequate supply of CAB becomes available is currently unknown. A separate regulatory document will provide instructions for implementation of supply of CAB for this purpose. Additionally, participants who have been lost to follow up and report to the site during the time that this Letter of Amendment is in effect will be offered CAB at the discretion of the Investigator of Record, per the instructions below.
- 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 083 Clinical Management Committee for guidance.
  - 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 for injection visits only. Separate safety visits two weeks following injection visits **WILL NO LONGER BE CONDUCTED; safety procedures and evaluations will be performed at injection visits only.**
  - 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 for injection visits only. Separate safety visits two weeks following injection visits **WILL NO LONGER BE CONDUCTED; safety procedures and evaluations will be performed at injection visits only.** These participants will be offered CAB when it becomes available.
  - Participants in Step 2 who reach the Week 153 visit during the time this Letter of Amendment is in effect will transition to Step 3 and be followed on the current Step 3 visit schedule. That is, participants receiving active CAB LA will receive open-label TDF/FTC per the current Step 3 visit schedule, and participants on active TDF/FTC will remain on it and be followed on the current Step 3 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 be referred to local HIV prevention services and transition to annual follow-up. 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 enroll in the upcoming full amendment of the protocol.
- Upon implementation of LoA #1, participants who choose to continue study follow-up as outlined above will follow the current applicable Step-associated Schedule of Procedures and Evaluations with three exceptions:
    1. Pill counts at Weeks 2 and 4 for participants in Step 1 will no longer be required.
    2. Separate safety visits for all participants on Step 2 will no longer be conducted; safety procedures and evaluations will be performed at injection visits only.
    3. For all participants, the interviewer-administered questionnaires and computer-assisted self-interviewing surveys will be completed one last time at the next scheduled visit at which these assessments are scheduled to occur. Following that visit, these assessments will no longer be administered.

**PROTOCOL SIGNATURE PAGE**

**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**

**DAIDS Document ID # 20725**

**Version 3.0**

**October 31, 2019**

**Letter of Amendment # 1, May 19, 2020**

**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

## Appendix I

### Sample HPTN 083 Participant Letter/Information Sheet

**PRINCIPAL INVESTIGATOR:** [Insert PI Name/Affiliation]

Dear HPTN 083 Participant:

The purpose of this letter is to share with you some important results from the HPTN 083 study that have become available after a recent Data and Safety Monitoring Board (DSMB) meeting. 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 083 Study:

The HPTN 083 study is being done at 43 sites in North and South America, Asia and South Africa. 4570 participants joined this study, including [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 as well as 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 May 14, 2020, the DSMB found that participants given daily TDF/FTC pills had three times the number of HIV infections than participants getting long-acting cabotegravir shots (real CAB, also called CAB LA). 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. The DSMB recommended to stop the blinded part of the study and that the results be made public. Stopping the blinded part of the study means that all participants will be told which study group they were put in when they joined the study.

The HPTN 083 study will continue. The study team wants you to keep coming to this clinic for follow up visits and procedures. For now, you will stay in the Group that you were put in at the beginning of the study. 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 part of the study where you are getting injections (Step 2), you will come to the clinic 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. The visits two weeks after the injection visits are no longer required for either group.

[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 the group that got real TDF/FTC and you want to get CABs, 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 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. 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 083 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 083 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 083.

Sincerely,

[Insert name and contact information of Investigator of Record]

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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