

**Final 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 2.0, dated 6 November 2019**

**DAIDS Document ID: 38070**

**IND #: 122,744**

**Final Letter of Amendment Version: 23 June 2020**

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This LoA both: 1) Clarifies the Qualitative Sub-study and 2) Formalizes guidance initially sent to HPTN 084 sites on 17 March and refined on 17 April 2020 and provides operational flexibility for conducting study visits and procedures when needed to ensure ongoing access to study drugs and to prioritize the conduct of clinically and scientifically important evaluations when possible.

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.

Implementation of this LoA is expected to be time-limited in relation to the COVID-19 pandemic. In consultation with HPTN Leadership and the study Sponsor, the HPTN 084 Protocol Team will determine when, in the future, the specifications of this LoA are no longer applicable. 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. Clarifications made to the Qualitative Sub-study
  2. Guidance on study conduct during the COVID-19 pandemic
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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.

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**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 #1, Dated 23 June 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. Clarifications made to the Qualitative Sub-study

## 2.5 Study Design and Overview

### Qualitative Sub-study:

A prospective, qualitative sub-study will be conducted at four sites to collect more in-depth information on women's preferences for and experiences with CAB LA versus other potential HIV prevention methods, and to better understand circumstances related to special cases such as pregnancy, **product disruption due to COVID-19**, early product termination or HIV seroconversion. The sub-study will include two sets of data collection activities: 1) a series of in-depth interviews with a total of approximately 104 participants (approximately 26 participants per site) who are each interviewed at a maximum of 3 timepoints; and 2) quarterly semi-structured observations conducted in waiting rooms or other public clinic venues where participants are gathered.

- 1) Repeated in-depth interviews: At each of the four sites, a subset of approximately 10-16 women will be invited to participate in a maximum of three in-depth interviews. **Women will be sampled to reflect early (2018), middle (2019) and more recent enrollment (2020) into the trial facilitating exploration of major events such as the dolutegravir and COVID-19 issues that affected trial implementation** ~~scheduled to take place after the first injection—coinciding with the end of Step 1, at one year of injectable use—middle of Step 2, and finally after transition to the open-label oral PrEP follow-up—Step 3.~~ In addition, up to 10 women per site who, over the course of the trial, become pregnant, **experience product or visit disruptions due to COVID-19 measures**, request to discontinue the study or terminate product use, or who seroconvert will be invited to participate in up to two interviews to explore women's reproductive choices or other circumstances affecting continued trial participation.
- 2) Waiting room observations: Approximately once a quarter, **as feasible**, a qualitative team member will conduct a 45-minute semi-structured observation in the waiting room(s) of the study clinic. The team will use a qualitative data extraction sheet to make notes about the overall demeanor of participants, topics of discussion and any information participants wish to share about their overall experiences, concerns, or recommendation related to the trial.

## 5.16 Acceptability Assessments

### Qualitative Sub-study

#### In-Depth Interviews (IDIs)

~~Approximately each quarter (once the qualitative study is initiated), at~~ The four sites participating in the qualitative sub-study **will work with SCHARP to randomly select and short-list from 8-10 participants who are currently enrolled and on study product across several years of trial implementation (e.g., Jan-Dec 2018; Jan-Dec 2019; Jan 2020 to present). Sites will enroll from 4-6 participants in each of these time periods to participate in the sub-study. If a site is still enrolling, it may choose to enroll fewer (e.g., 4-5) participants each from 2018 or 2019, and more participants (6-8) from 2020.** ~~, two participants who have successfully completed the five-week oral run-in and obtained their first injection will be invited to participate in the qualitative sub-study.~~

**They IDIs may be conducted remotely (by cell phone or video chat) or be conducted in another private and mutually agreed upon location in sites that are limiting non-essential clinic visits. Sub-study participants who participate in IDIs will be consented separately and must agree to being interviewed up to three times over the course of their trial participation.**

~~Up to two interviews will be conducted during the Injection phase.~~ **If an interview takes place virtually, informed consent will be documented in a manner that is consistent with local ethics committee or IRB guidelines. Several options may be considered including administering and recording the informed consent document, as well as the participant's verbal consent over the phone and documenting consent in a separate document, or using an approved mobile application, such as the FDA-approved MyStudies to obtain and transfer a secure signature from the participant (see <https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app>.)**

Topics for the ~~first interview, occurring approximately between week 5 and 12 (1<sup>st</sup> and 2<sup>nd</sup> injection), include:~~ **recently enrolled participants (within 1<sup>st</sup> or second injection):**

- Household, relationship context, **including any impact of COVID-19;**
- Current and future goals, including perspectives on delaying fertility during trial;
- Perceived HIV risk;
- Current/previous experience with prevention products – contraception, condoms, other HIV prevention methods, **including how local response to COVID-19 affected product use;**
- Motivation for trial participation, including knowledge of and decisions related to joining HPTN 084 versus other HIV prevention trials;
- Disclosure to partner(s), family, friends about trial;
- Understanding of trial context – randomization, blood draws and other criteria;
- Beliefs about trial products;
- Understanding of and concerns about pregnancy restrictions;
- Experience with oral pill use and with first injection.

Topics for the ~~second interview, occurring approximately between week 37 and 45 (5<sup>th</sup> and 6<sup>th</sup> injection), include:~~ **experienced participants (in Step 2, but have received five or more injections):**

- ~~Changes in~~ Household/relationship context, or any changes if previously interviewed;
- Any significant life events, **including how local response to COVID-19 affected household/daily routine and trial participation;**
- Partner/other support or lack for trial participation;
- Attitudes towards aspects of trial participation, including interactions with trial staff;
- Adherence to oral pills – focused on reasons for missing pills;
- Adherence to injections – focused on getting to clinic, acceptability of injection;
- **Any impact of service disruption due to COVID-19 on product adherence;**
- Acceptability of oral pills versus injectable prevention;
- Perceived HIV risk;
- Reproductive desires, contraceptive experiences and thoughts about pregnancy restrictions;
- Early preferences for prevention modalities and any other suggestions or concerns about the trial.

The ~~third and final in-depth interview will be conducted approximately within a month of the participant moving into the phase 3 follow-up on open-label TDF/FTC~~ **while participants are still in active follow-up but have been unblinded to the product they are using (e.g., if an individual or the trial moves to an open-label TDF/FTC).** Topics for this interview include:

- Any significant life events, **including how local response to COVID-19 affected household/daily routine and trial participation;**
- Participant thoughts about which arm she was in, Participant thoughts about level of adherence;
- Perceptions about pregnancy restrictions for CAB LA;
- Perceptions of, questions about the open-label arm;
- Presentation of results (if available) and any discussion about discordance – explore barriers and facilitators of adherence, **including any impact of COVID-19 on product adherence;**
- Recommendations about how to better support access and adherence to prevention methods beyond trial;
- and Preferences for prevention beyond trial setting.

Additional topics for participants recruited as “special cases” include:

- Feelings toward and circumstances related to pregnancy, product discontinuation or seroconversion;
- Partner and family member attitudes towards pregnancy and/or product use;
- **Impact of COVID-19 related clinic, community or household disruptions on trial participation, product use or general well-being**
- Attitudes towards product unblinding as related to pregnancy or seroconversion;
- Attitudes towards using CAB LA and/or TDF/FTC during pregnancy;
- Prevention preferences beyond trial and any recommendations;
- treatment or care plans, if related to seroconversion.

#### Waiting room observations

Approximately once a quarter, a qualitative team member will conduct a 45-minute semi-structured observation in the waiting room(s) of the study clinic until data saturation. **(This activity may take place less frequently if COVID-related policies suspend use of waiting rooms for study participants.) Because information about potential waiting room observations was included in the main study consent, no additional consent procedures are required for this activity.** The qualitative team will use a data extraction sheet to note:

- Date/time; Approximate # of participants in waiting room, including gender and any babies, children;
- Materials, videos or other activities organized by site;
- Overall activity within waiting room;
- Focus on a nearby cluster of participants – overall demeanor of individuals (animated, calm, happy, bored, irritated) and topics of discussion if overheard;
- If any brief intercepts with participant, information about wait time in clinic, overall experience in trial, concerns, recommendations or other thoughts shared with observer.

#### 7.8.1 Analyses of Primary Efficacy Objective

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. **As outlined in greater detail in the Statistical Analysis Plan, version 2.0, dated June 9, 2020, and the HPTN 084 COVID Disruption document, prespecified intervals of COVID-19 disruption may be administratively censored from the analysis using the Anderson-Gill counting process formulation of the Cox model.** We will test the

hypothesis  $H_0$ : HR = 1.0 versus  $H_a$ : HR  $\neq$  1.0 using  $\alpha = 0.05$ . **If the number of events is small (<40) then the p-value will be confirmed using a permutation test based on 100,000 random permutations of the treatment assignments; if there is a meaningful difference between the permutation and asymptotic procedures, the permutation p-value will be used.** Treatment efficacy will be estimated as TE = 1 - HR.

## 2. Guidance on study conduct during the COVID-19 pandemic

Table of Contents has been updated adding Appendix VI: Guidance on study conduct during the COVID-19 pandemic

### Appendix VI: Guidance on study conduct during the COVID-19 pandemic

#### PRIORITIZATION OF STUDY VISIT PROCEDURES

- Sites with full capacity to conduct study visits in-person at the study clinic should continue to do so in full compliance with the protocol.
- Sites with limited capacity to conduct in-person study visits should prioritize assessments as determined by the site Investigator of Record (IoR) (e.g., urgent safety testing, HIV testing, provision of study product, etc.).
- Sites with no capacity to conduct in-person visits may conduct telephonic or video-based assessments remotely at the discretion of the IoR (and following all institutional approval requirements), and may include targeted medical history (including ascertainment of AEs), HIV and adherence counseling, interviewer administered surveys, etc. The content of these visits should be determined by the site IoR.

Note: If locally available, feasible, and at the discretion of the IoR, home HIV self-tests can be sourced and distributed to participants for participant use, and results demonstrated by video or photo-sharing to study sites as corroborative evidence of testing and test results. Such photos should be placed in the participant research record. Absence of home-testing results will NOT be considered a protocol deviation, nor reportable.

- Sites that are able may also conduct study visits — in full or in part — off-site if permitted by applicable government, health authority, and institutional policies. This is including but not limited to home-based visits. Where this option is permitted, site staff should communicate with participants to determine in advance where and when such visits will take place, with adequate protections for safety, privacy, and confidentiality. Offsite visit procedures should be conducted by site staff who are adequately qualified and trained to conduct the procedures, as determined by the site Investigator of Record (IoR), with attention paid to occupational health, biohazard containment, and specimen and data chain of custody. These staff should also be adequately qualified and trained to immediately assess and/or manage any adverse events or social impacts that may occur during the visits. If adverse events requiring further evaluation or management are identified during an off-site visit, staff conducting the visit should arrange for appropriate clinical management, in consultation with the IoR or designee as needed. NOTE: Step 2 BLINDED study product cannot be provided at an off-site visit.

#### Finalized Guidance for STEPS 1, 2 and 3 sent out 17 April 2020

These recommendations are made with the goal of ensuring both participant and staff safety and respecting the public health recommendations to minimize disease transmission.

1. Screening and enrollment were paused until further notice at all sites effective close of business local time Tuesday, March 17, 2020. This meant that any screening and enrollment appointments scheduled had to be deferred until after the pause was lifted on 28 May 2020.
2. For participants on study, follow-up visits should continue to ensure safety of the participants in alignment with local guidance and protocol where possible. We encourage all sites to plan for contingencies regarding HPTN 084 participants on study.
3. In the event that CRS operations are diminished or suspended entirely, and where conduct of study visits is not possible either because of staffing or operational concerns, please note the following:
  - a. For participants in Step 1 (applicable to sites in South Africa and Eswatini), we recommend that where safe and feasible, participants be transitioned to step 2. At some sites, it may be possible to conduct week 4 testing and receive same-day results. In this case, sites may then proceed to complete week 5 procedures at that visit if protocol requirements for transition to step 2 are met.

Where it is not possible to complete week 4 visits, participants should continue study product. Site staff should provide participants with sufficient product to cover this time period and ensure that they have sufficient contraceptive protection. Please counsel participants on the need to adopt additional HIV and pregnancy preventive measures if they are unable to return to site per schedule, and to record their pill taking and when that ended. We will follow routine procedures for assessing the transition to step 2 for delayed week 4/5.

We do not anticipate significant product-related adverse events during this period, but if participants report significant symptoms, they should contact the site by phone. The IoR may consult the CMC, but in case responses are delayed, the IoR may use clinical judgement to hold or continue product.

- b. For participants in step 2: Sufficient product should be provided to cover the 8-week interval between injections plus a buffer of 30 days per the SSP - even for visits prior to week 41. This may allow the visit interval to extend up to 12 weeks. Contraception coverage should be verified to cover the entire interval.

Participants need to receive both blinded study products during step 2. If injections cannot be administered, oral product should also be held. In this scenario, participants are advised to take additional measures to prevent HIV infection and exposure by all means available until they can return to study site. If they use non-study provided open-label PrEP during this period they should be encouraged to keep a log of dates of use should they use this option.

- c. For participants in step 3: we recommend continuation on daily unblinded oral product. Where participants cannot report for quarterly visits, participants should continue study product and where possible sites should explore delivery of product directly to participants from site investigational pharmacies. If not feasible, participants should be counselled to use other available means to protect themselves against HIV exposure and infection and pregnancy prevention until they are able to return to study participation. IoRs can use their judgement about ongoing dispensation of oral product in these extraordinary circumstances

without routine HIV and creatinine testing, based on known previous renal function, risk and adherence. Self-testing for HIV may also be useful in this setting if practical. The same guidance would apply to pregnant participants.

- d. For participants in step 2 where early pregnancy cannot be excluded including a lapse in contraception, we suggest providing the participant with up to four weeks of TDF/FTC. The site can provide the participant with a pregnancy test kit to repeat pregnancy testing at home. Where the second test is negative, see guidance re step 2. Where the test is positive, see guidance re step 3.
  - e. For annual follow up: Annual visits should be delayed until study conduct can be resumed at the site.
4. **PLEASE NOTE:** These measures may not all be needed at your site immediately and are to be deployed as needed. Before any of these above is implemented, and should you update your plans, please inform the people copied on this email, including your site-specific DAIDS OCSO Program Officer. Please note that additional guidance was issued to CTU PIs and CRS leaders regarding considerations for visits during this extraordinary time (see attachment).
  5. Please follow Data Communique #8, sent on 2 April 2020, regarding data collection procedures and documentation of missed visits or missed procedures, and any associated protocol deviations.
  6. Please consider whether partial or full participant reimbursements may be provided for telephonic visits during this pandemic. This decision must be made in conjunction with your IRB and CTU.
  7. Finally, as the situation unfolds in our countries, sites will also need to consider procedures for symptom screening, isolation of suspected cases and linkage to testing based on national guidelines. It may be useful to anticipate these contingencies ahead of time.

#### **STUDY PRODUCT CONSIDERATIONS**

- For emergency cases, and if possible given local considerations, the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks permits shipment or courier of oral study product from the site directly to participants. The pharmacist should refer to the section on “Shipping Study Product to a Participant” in this manual for detailed procedures. If this method is to be implemented, each site pharmacist must develop appropriate procedures for the shipment or courier of oral study product to identified participant in accordance with these guidelines and must include appropriately documented chain of custody. This method should only be used if permissible per local institutional and IRB/EC policies.
- All questions related to study product management should be directed to Katie Shin – [kashin@niaid.nih.gov](mailto:kashin@niaid.nih.gov).

#### **DOCUMENTATION**

- Site-specific contingency plans, and the implementation thereof, should be documented in essential document files for HPTN 084.



- **Participant-specific documentation should be entered in participant study charts in real-time to the extent possible.**
- **Specific guidance regarding coding visits and instructions therein is forthcoming from SCHARP in a separate communication to all sites.**
- **In consultation with the Division of AIDS, the HPTN Network is developing comprehensive guidance for documenting and/or reporting protocol deviations that may occur due to limited site capacity to conduct study visits or procedures during the COVID-19 pandemic. Once this Network-level guidance is available, it will be provided in a separate communication to all sites.**