**Letter of Amendment # 3 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 1.0, February 2, 2016**
**DAIDS Document ID: 20725**
**IND # 122, 744**

**Final Version of LoA # 3: 10 November 2016**

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study, including the study informed consent forms, and must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their 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 and all required approvals of protocol Version 1.0, LoA # 1, LoA # 2, **and** this LoA # 3 must be obtained before initiating this study. Likewise, all participants must provide written informed consent for this study using site-specific informed consent forms that correspond to this LoA.

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. This notification must be received prior to implementation of this LoA. Receipt of this notification, as well as an initial registration notification for protocol Version 1.0, will be confirmed as part of the site-specific study activation process for this study.

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 083.

If the HPTN 083 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.

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## Summary of Revisions and Rationale

**Revision 1 a -c**: The background section of the protocol has been updated to include data from the ViiV Healthcare-sponsored ÉCLAIR study that was presented as an oral abstract during the HIV Research for Prevention (HIVR4P) conference in Chicago, Illinios, USA, in October 2016. The data showed that in ÉCLAIR, which randomized US-based men to three sequential intramuscular injections of 800 mg of CAB LA or placebo (administered as 2 x 400 mg) every 12 weeks, approximately 17% of the study population on active drug had detectable cabotegavir drug levels at 52 weeks after the last injection of cabotegravir. Levels ranged between 29 and 105 ng/ml. These levels are between the lower limit of assay quantitation (25 ng/ml) and 1 x PA-$IC_{90}$ (166 ng/ml) Available data prior to the analysis of these new data indicated that detectable drug could persist up to 52 weeks after final injection.

**Revision 2**: The references have been updated to add the abstract outlined in Revision 1.

**Revision 3 a-b**: The sample informed consent form in Appendix IV has been modified per Revision 1, as well as per a recommendation from the NIAID Multinational Data and Safety Monitoring Board (DSMB). The protocol chair and protocol statistitians met with the DSMB on November 1, 2016 to present the overall study design and statistical and monitoring plans. The DSMB recommended that the risk section of the sample informed consent form be revised to include specific risk language about what is known (or unknown) about HIV acquisition likelihood for each study product.

**Revision 4 a-b:** Section 5.11 of the protocol erronesously states that participants who are unable to receive the first injection for any reason will be terminated from the study. This has been corrected to indicate that participants in Step 1 who are unable to transition to Step 2 for any reason other than HIV infection will be followed annually for HIV testing until the conclusion of Step 2 of the study. Information also has been added regarding stopping injections and confirmed HIV infection for participants in Step 2, as well as instructions for participants in Step 3 that become HIV infected. Appendix II has been corrected regarding which group to contact if a participant becomes HIV-infected during the study.

**Revision 1a** Section 1.3.2 – CAB LA

Following a single IM or subcutaneous (SC) injection of CAB LA, plasma drug concentrations increased rapidly over the first week, followed by a general trend to plateau for the remainder of the 12-week follow-up period. ~~The drug was detected in plasma up to 52 weeks, and the mean absorption-limited apparent terminal phase half-life ranged from 21 to 50 days, reflecting absorption from depot site rather than elimination from the systemic circulation.~~ **Data from the ÉCLAIR study (which administered three serial injections of 800 mg CAB LA IM every 12 weeks [as 2 x 400 mg IM at each injection]) have shown that in some individuals (14 out of 83, 17%), CAB was detectable in plasma at 52 weeks post last injection [80]. The CAB concentrations in these study participants ranged from 29-105 ng/ml; these values fall between the lower limit of quantiation (LOQ) of 25 ng/ml and 1 x PA-$IC_{90}$ (166 ng/ml).**

**Additional data through 76 weeks post last injection (an additional 24 weeks longer than the current follow-up of 52-weeks post last injection) in HPTN 077 (which administers CAB LA 800 mg IM every 12 weeks in Cohort 1 and CAB LA 600 mg IM every 8 weeks after two initial injections four weeks apart in Cohort 2) will be available in approximately the fourth quarter of 2017 (for Cohort 1) and the third quarter of 2018 (for Cohort 2). These data will provide additional insight into how long cabotegravir levels may be detected after terminal injection, and help to inform the optimal duration of Step 3 of HPTN 083.**

**Revision 1b** Section 1.4 – Clinical Experience to Date: Oral CAB and CAB LA

**Footnote h in Table 2: Cumulative Cabotegravir Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up To 01 July 2015**

Note: Only footnote "h" is depicted.

h. Detectable CAB concentrations can remain for ~~up to 52 weeks~~ **as long as a year or more** following the last CAB injection. **See Section 1.3.2.**

**Revision 1c** Section 1.12 – Rationale for use of oral lead-in prior to injectable dosing

The CAB LA formulation has a pharmacokinetic decay rate that exposes the injected individual to detectable levels of cabotegravir for up to ~~52 weeks~~ **a year or more** after an injection **(see Section 1.3.2).** In order to maximally identify any acute toxicity prior to administration of a non-dialyzable, non-removable depot injection, a 5-week lead-in period of daily oral (short acting) cabotegravir will be employed. This lead-in period will be evaluated with serial safety assessments prior to injectable administration. The current plans for product labeling should FDA approval be granted include an oral lead-in strategy when adequate safety is established after 4 weeks of oral drug exposure. The 5-week exposure in this study is designed to provide uninterrupted study product coverage while awaiting return of the Week 4 safety laboratory assessments.

**Revision 2** Section 11: References

Reference number 80 has been added as follows:

**80. ECLAIR Study of Cabotegravir LA Injections: Characterization of Safety and PK During the "PK Tail" Phase. Ford S; Stancil B; Markowitz M, et al. HIV Research for Prevention, Chicago, IL, USA, October 17-21, 2016. Abstract OA12.06LB.**

**Revision 3a** Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: Only the fourth (4th) paragraph under "RISKS AND/OR DISCOMFORTS, Study Medications, The side effects of cabotegravir include:" is impacted and is depicted below.

The shots you receive in this study are long acting, meaning they stay in your body for a long time **– as long as a year or more.** ~~One single shot can stay in your body for up to one year.~~ If you develop a side effect to the study drug after the shot, there will be no way to remove the drug from your body. If you are in Group A, the group that gets the real CAB, we will monitor your health for a year after your last injection. If you get infected with HIV while on the real CAB, it is possible that real CAB and other HIV drugs that are like it may not work to fight the virus.

**Revision 3b** Appendix IV: Sample Screening and Enrollment Informed Consent Form

Note: The "HIV Infection" section under RISKS AND/OR DISCOMFORTS is impacted and is depicted below.

**HIV Infection**

**We told you earlier that we do not know if CAB works to protect you from getting HIV. If you are in the group that gets the real CAB, you still may be at risk of getting HIV. We do know that taking TDF/FTC every day can be very effective at preventing HIV infection. If it is not taken every day, you may not be well protected. Because of these risks, it is very important that you use condoms every time you have sex, no matter what group you are in.**

Because the study medication is itself being studied to be an HIV treatment medication, if you become HIV infected while taking the study medication, there is a chance that other drugs used to treat HIV infection might not work. This is called drug resistance.

To reduce the possibility of developing drug resistance, you will be asked to work with your local study clinic team to begin HIV treatment after your last study medication injection. The study will not provide this treatment but may be able to help you find and/or pay for that treatment.

**Revision 4a** Section 5.11 Procedures for Participants Who Do Not Complete the Full Course of Injections

Participants on either arm who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open-label TDF/FTC according to Step 3 Arm A assessments; such participants will remain blinded to their original randomized assignment.

Participants **in Step 1 of the study** who are unable to **transition to Step 2 of the study** ~~receive the first injection~~ for any reason **other than HIV infection** will be ~~terminated from the study~~ **followed on an annual basis until the conclusion of Step 2 of the study (refer to SSP Manual)**. **Participants with confirmed HIV infection during Step 1 of the study** ~~**If** the reason is due to HIV infection, those participants~~ will **not transition to Step 2 of the study, but will** be referred to care and will be terminated from the study.

**Participants in Step 2 of the study that no longer receive injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.**

**Sites should contact 083HIV@hptn.org for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.**

**Revision 4b** Appendix II: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

Only the note included in this appendix is depicted below.

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who become infected at any time during the study. The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Step 2 of the study. Participants with confirmed HIV infection in Step 3 of the study may undergo similar procedures as listed in Weeks 12, 24, 26, and 48, and will be determined by the **members of 083HIV@hptn.org** ~~**CMC**~~**.**