

**Final 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 3.0, October 31, 2019**

**DAIDS Document ID: 20725**

**IND # 122, 744**

**Letter of Amendment #3: July 23, 2020**

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study 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.

As this LoA does not impact any study procedures, assessments or the sample informed consent form, no action is needed on the part of the sites except for 1) signing and dating the protocol signature page by the Investigator of Record; 2) obtaining all relevant IRB/EC/other regulatory entity approvals; and 3) submission of 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 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 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 **bold** will be added, and text appearing in ~~strike-through~~ will be deleted (all changes also highlighted in yellow).

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## Summary of Revisions

The modifications included in this protocol amendment are summarized directly below and detailed in the 'implementation' section that follows.

Revision 1: Updated Protocol Signature Page for this Letter of Amendment #3.

Revisions 2 and 3 were inadvertently not included in Letter of Amendment #2, dated July 1, 2020, to Protocol Version 3.0. These updates are made to achieve alignment between Protocol Version 3.0 and the Statistical Analysis Plan, Version 3.0, dated July 1, 2020. The Statistical Analysis Plan will not be submitted to sites for review; it is referenced here only for regulatory purposes. Language in Protocol Section 7.11.1, Analyses of Primary Efficacy Objective, is updated to reflect these changes.

Revision 2: As the protocol was originally written, it was expected that every randomized participant would receive oral study product. Because of pharmacy capacity at some sites, some participants were randomized and never received study product but are still properly included in the modified intent-to-treat (mITT) cohort.

Revision 3: The protocol originally proposed to have TDF/FTC measure of adherence for the TDF/FTC arm, and injection for the CAB-LA arm. However, measures of TDF/FTC concentrations are only available in the adherence cohort, a randomly selected subgroup of 400 participants in the TDF/FTC arm, and pill counts and dispensing were not interpretable as precise adherence measures in the TDF/FTC arm. Injections were accurately recorded in both arms, and these are used as a consistent metric for adherence to blinded study product that is precise, consistently recorded and comparable between arms. The change to estimation of efficacy for time periods where participants remained on blinded study product and compliant to the injection schedule mitigates the risk of bias due to potentially different adherence assessments in each arm.

## Implementation

Modifications of protocol text are described below. Modified protocol text is shown using ~~strikethrough~~ for deletions and **bold** type for additions.

### Revision 1: Protocol Signature Page

The protocol signature page is updated for Letter of Amendment #3 (see next page).

**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**

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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**

## Revision 2:

### 7.11.1 Analyses of Primary Efficacy Objective

The first paragraph under the first bullet is impacted and is depicted below.

**MITT:** A modified intent-to-treat will be used as the primary assessment for the efficacy comparison, thus all participants **who receive at least one dose of oral study product** will contribute to the primary analyses. Any participant determined to be HIV infected prior to receiving study product will be omitted from the analysis.

## Revision 3:

### 7.11.1 Analyses of Primary Efficacy Objective

The last paragraph and accompanying bullets are impacted and depicted below.

**On blinded study product-Per protocol: An on blinded study product** A per protocol estimate of treatment efficacy will be conducted as a secondary analysis in the non-inferiority context of active control, as a verification that a similar HR estimate is obtained **in the compliant population in** participants who are HIV-uninfected at the time of the first injection, while participants are compliant to the injection schedule. Compliance will be defined as: **receiving the second injection within 6 weeks of the first injection and all subsequent injections within 10 weeks of the prior injection.** Adherent by administration and plasma TDF concentrations: In CAB LA arm, from the time of receipt of the injection the participant is considered adherent for 8 weeks. In the TDF/FTC arms, from time of dispensing pills the participant is considered adherent if plasma TDF concentrations are detectable at 8 weeks. Each HIV testing interval (time period between determining HIV status through study testing) will be defined as compliant if participant has TDF levels consistent with 4 or more doses per week by appropriate pharmacokinetic laboratory assays.

Estimates will be computed as follows:

- **Time varying compliance:** Compliance will be a time dependent covariate, and the HR for efficacy CAB LA vs TDF/FTC during periods of compliance will be estimated using Cox proportional hazards with an interaction term between study arm and compliance. The estimate of efficacy will be the HR for CAB LA vs TDF/FTC in the compliant periods.
- **Estimate in the compliant cohort:** The compliant cohort is defined as those participants who were adherent >80% of their time on study. The same methods as detailed for the primary analysis will be used for estimating effectiveness on the compliant cohort. Evidence of confounding in this cohort will result in an analysis that is adjusted for additional baseline risk covariates.

**Per protocol: A per protocol estimate of treatment efficacy, excluding participants with major protocol violations, or participant time after a major protocol violation, will be conducted as a secondary analysis in the non-inferiority context of an active control, as a verification that a similar HR estimate is obtained.**