Final Letter of Amendment #2 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 # 2: July 1, 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).

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 # 2.

Revision 2: In light of the impact of the global COVID-19 pandemic on the ability of many of the HPTN 083 participating sites to continue implementing the protocol as designed, the protocol team changed the interim monitoring criteria for HPTN 083 to recommending stopping the study if clear evidence of non-inferiority is shown rather than the originally proposed plan to stop early only with evidence of superiority. As such, language in the third paragraph of Section 7.6 of the protocol, Sample Size and Interim Monitoring, is updated to reflect this change. This update is made to be consistent with the HPTN Interim Monitoring Plan, Version 2.0, dated May 8, 2020, as well as the Statistical Analysis Plan, Version 3.0, dated July 1, 2020, and now harmonizes all three documents. Neither the HPTN Interim Monitoring Plan nor the Statistical Analysis Plan will be submitted to sites for review; they are referenced here only for regulatory purposes.

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 #2 (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:

7.6 Sample Size and Interim Monitoring

The third paragraph in this section is impacted and is therefore the only paragraph depicted below.

Interim monitoring will be conducted by an independent DSMB on a regular schedule, with safety review approximately every 6 months, and at least annually. Formal interim analyses will be planned approximately 4 times during the study, using the Lan-DeMets modification of the O'Brien-Fleming stopping bounds to control alpha spending. ~~Superiority~~ **Non-inferiority** bounds will be used for early stopping for favorable risk-to-benefit ratio for CAB LA **compared to TDF/FTC.** ~~; non-inferiority bounds will be used for early stopping for unfavorable risk-to-benefit ratio. Thus, the study will continue if non-inferiority is established but superiority remains plausible, however the study may end early if non-inferiority is ruled implausible or if inferiority is established.~~ **Stopping will also be advised if there is early evidence that CAB LA is clearly not as effective as TDF/FTC (i.e., early evidence that HR>1.0).**