

FINAL Letter of Amendment # 2 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: 10 September 2020

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.

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. The Protocol Team Roster has been updated.
2. The Introduction, References, and Informed Consent sections of the Protocol have been updated with the most recent information regarding CAB and CAB LA from HPTN 083 results.
3. The mobile app MyStudies is not available internationally and has been removed as a choice for consenting participants.
4. A provision for the SRC reviewing every subsequent protocol version has been removed. This has not been HPTN policy and was an erroneous holdover from a protocol template.
5. BMI is to be calculated from Baseline forward to assess objectives as well as needle size. This has been clarified in the Schedule of Evaluations.

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.

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
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A Study of the HIV Prevention Trials Network (HPTN)

FINAL Letter of Amendment #2, Dated 10 September 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. Protocol Team Roster

PROTOCOL CHAIR:

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Research Professor and Director: Research

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2. Updates due to recent HPTN 083 results

1.0 INTRODUCTION

1.6 Clinical Experience to Date Oral CAB and CAB LA

Plasma drug concentrations after administration of CAB LA are expected to remain between the oral CAB 10 mg and 30 mg exposures. At this stage of development, a lead-in of oral CAB is being employed to determine safety and tolerability in individual participants, prior to the transition to CAB LA. The accumulated efficacy and safety data with oral CAB and CAB LA in HIV-infected and HIV-uninfected participants supports continued clinical development for HIV treatment and PrEP.

In May 2020 at a pre-planned interim review the DSMB recommended that the blinded portion of HPTN 083, a companion phase III trial of CAB LA for HIV prevention in MSM and transgender women (TGW), be stopped for evidence of efficacy. Subsequent analysis confirmed that CAB was superior to TDF/FTC (HR 0.35; 95% CI 0.18-0.62) in preventing HIV infection. Overall incidence was 0.81% (95% CI 0.61- 1.07). CAB and

TDF/FTC were both well tolerated; most adverse events were mild/moderate and balanced between arms. Injection site reactions were more common in the cabotegravir arm but were generally grade 1-2 and decreased with time on study. Injection intolerance led to discontinuation in 46 (2.2%) active CAB-LA recipients and was associated with the severity of the reaction. Grade 2+ events observed with significant higher frequency in the CAB LA arm included nasopharyngitis, increased blood glucose and pyrexia. These differences were not observed when compared grade 3+ events. There were no significant differences in serious adverse events between the two groups.⁴⁵

1.7.1 Dolutegravir and Pregnancy

Dolutegravir (DTG) is an integrase inhibitor in the same class of pharmaceuticals as CAB. Thus far, limited safety or efficacy data for DTG in pregnancy in humans have been published or presented.

In May 2018, WHO and several other regulatory agencies released advisories regarding the safety of dolutegravir in early pregnancy based on an interim review of data from the Botswana NICHD-funded Tsepamo Birth Outcomes Surveillance Study, in Botswana.⁴⁷ This study was designed to evaluate adverse birth outcomes by maternal HIV status and ART regimen, and to determine whether there is an increased risk of neural tube defects (NTDs) among infants exposed to efavirenz (EFV) from conception. Botswana's HIV program moved to universal ART with DTG/TDF/FTC in first line for patients starting ART (including pregnant women) in May of 2016 (women already on other regimens were not switched to DTG). The previous first-line regimen was EFV/TDF/FTC. Almost all women on DTG-based and EFV-based ART took these drugs in combination with TDF/FTC.

More than 95% of women in Botswana deliver in a hospital, and obstetric records were available for >99% of women. The Tsepamo surveillance study was initially conducted at 8 of the largest public maternity wards across Botswana (representing ~45% of the total births in the country), and after the interim review in May 2018 expanded to a further 10 sites from July 2018 (increasing coverage to approximately 72% of all births). Research assistants abstracted exposure data from the maternity card for all consecutive in-hospital deliveries (both HIV-infected and HIV-uninfected women). Each newborn, whether stillborn or live-born, underwent a systematic infant surface examination that was completed by trained nurse midwives. Reports and photographs (where available) of major abnormalities are reviewed by an experienced medical geneticist who was blinded to exposure information. During a preliminary unscheduled analysis of the Tsepamo data collected between August 15, 2014 and May 1, 2018, which was undertaken at the request of colleagues who were preparing for a WHO meeting, the investigators found 4 cases of neural tube defects in babies of 426 women who became pregnant while taking DTG (prevalence 0.9%). This is compared to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

A recent published has provided an updated analysis of 119,033 deliveries from August 2014 through to March 2019. Overall, among 1,683 deliveries in women taken dolutegravir at conception, 5 neural tube defects were found (0.30%, 95% CI 0.13-0.69) i.e. one additional case observed since May 2018, in comparison to 15 neural tube defects observed in 14,792

deliveries (0.10%, 95% CI 0.06-0.17) in women taking non-dolutegravir ART at conception. Since the initial 2018 report, the estimated prevalence has diminished in magnitude to approximately 3 per 1000 births but remains greater than for all other types of antiretroviral exposure at conception, although the absolute risk difference is relatively small at 2 per 1000 exposures.⁴⁸ Since August 2014, the Tsepamo study collected information on 153,899 deliveries. An updated analysis including births since March 2019 reported seven neural tube defects among 3,591 women exposed to dolutegravir at conception (0.19, 95% CI 0.09%, 0.40%). In comparison, neural tube defects occurred in 21/19,361 (0.11%; 95% CI 0.07%, 0.17%) women on any non-dolutegravir regimen at conception. The prevalence of neural tube defects did not differ significantly between dolutegravir and any non-dolutegravir antiretrovirals from conception (0.09% difference; 95% CI -0.03%, 0.30%). After a period of decline since the original safety signal, the prevalence of neural tube defects in infants born to women on dolutegravir around the time of conception appears to have stabilized at 2 per 1000.⁴⁹

11.0 REFERENCES

45. Landovitz R, Donnell D, Clement M, et al. HPTN083 interim results: Pre-exposure prophylaxis (PrEP) containing long-acting injectable cabotegravir (CAB-LA) is safe and highly effective for cisgender men and transgender women who have sex with men (MSM,TGW). AIDS 2020. Virtual.
47. Zash R, Holmes L, Diseko M, et al. Neural Tube Defects and Antiretroviral Treatment Regimens in Botswana. New England Journal of Medicine 2019.
49. Zash R, Holmes L, Diseko M, et al. Update on neural tube defects with antiretroviral exposure in the Tsepamo study, Botswana. AIDS 2020. Virtual.

Appendix IV: Sample Screening and Enrollment Informed Consent Form

PREGNANCY

We do not know if CAB can cause birth defects in babies. Birth defects have not been found in any animal studies of CAB so far. We have information from a different study conducted in Botswana with dolutegravir (DTG), a medicine that is similar to but not the same as cabotegravir (CAB), the medicine being studied in HPTN 084. In that study, some women living with HIV were taking DTG for treatment of HIV infection around the time of conception. That study, known as the Tsepamo study, collected information on **119,033 153,899 deliveries at 18 government hospitals throughout** in Botswana from August 2014 to **March 2019 April 2020** and reported on babies that had birth defects of the spinal cord and brain (neural tube defects). These defects occur early on in the development of the pregnancy. **The latest results show that about 2 out of 1000 infants born to women who used DTG around the time of conception had a neural tube defect, compared to 1 in 1000 infants born to women using any non-DTG regimen. The difference between the two groups is not statistically significant.** When this new unexpected finding was first reported in May 2018, there were concerns that the rate of nervous system defects in babies of mothers using dolutegravir at the start of pregnancy was much higher than for other antiretroviral drugs.

However, we now know that the difference in the rate of these birth defects between the two groups is **essentially the same**.
~~Scientists are still investigating possible reasons for these findings.~~

BENEFITS

TDF/FTC is known to protect people from getting HIV if taken daily as directed. ~~However,~~
The recent results from the HPTN 083 study comparing CAB to TDF/FTC conducted in men who have sex with men and transgender women at 43 sites globally showed that participants given daily TDF/FTC pills had about three times the number of HIV infections compared to participants getting long-acting CAB. CAB has not yet been shown to protect against HIV infection in cisgender women, which is the reason we are doing this study.

3. MyStudies app has been removed

5.16 Acceptability Assessments

Qualitative Sub-study

The 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. 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>.)~~

4. Protocol Review and Approval

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent form contained in Appendix IV ~~and any subsequent modifications~~ will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent forms, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

5. BMI at each visit except Screening

Appendix Ia: Schedule of Evaluations – Screening and Step 1, Oral Run-in Phase

	Screening	Step 1		
		DAY 0/ Enrollment	WEEK 2	WEEK 4
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
Locator information	X	X	X	X
Demographic information		X		
Randomization		X		
HIV prevention counseling	X	X	X	X
Offer condoms	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		X		
CLINICAL EVALUATIONS & PROCEDURES				
Dispense study product (enough for 5 weeks)		X		
Observe participant take oral study product ¹		X	X ¹	X ¹
Adherence counseling/contraception counseling ¹³ /pill count (pill count Weeks 2 and 4 only)		X	X	X
Medical history (including bleeding history at Screening), contraceptive use, con meds, physical exam (with pulse, BP, weight and BMI calculated at each visit) ²	X	X	X	X

² Full physical exam is to be conducted during Enrollment. A targeted physical exam will be done at all other visits. Participant pulse, blood pressure and weight must be recorded at every visit. BMI must be calculated **at all visits except Screening**.