HIV Prevention Trials Network

Letter of Amendment #3 to:

HPTN 083-01

Safety, Tolerability and Acceptability of Long-Acting Cabotegravir (CAB LA) for the Prevention of HIV among Adolescent Males – A sub-study of HPTN 083

DAIDS Study ID: 38654

Protocol Version 3.0, dated 02 July 2021

Date of Letter of Amendment: 15 August 2022

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

Name of Investigator of Record
(printed)

HIV Prevention Trials Network

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The following information impacts the HPTN 083-01 study and must be forwarded to all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs before implementation.

The information contained in this LoA does impact the informed consent forms (ICFs).

Upon receiving final IRB/EC approval for this LoA, sites should implement the LoA immediately. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). As part of the registration package, sites must submit the Letter of Amendment Investigatory Signature Page, signed and dated by the Investigator of Record. Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with the LoA and any IRB correspondence should be retained in the site's regulatory files.

If the full HPTN 083-01 protocol is amended in the future, the changes in this LoA will be incorporated into the next version.

Summary of Revisions and Rationale

1. Revisions 1, 5, 6, 7, and 8: Changes were made to Sections 5.6, Appendices II and III (Schedules of Evaluations), and Appendices VII and VIII (ICFs) to remove specific length of time for prescription of TDF/FTC for Step 3, if oral PrEP is chosen by a participant. This change was made in order to allow flexibility for providers, while also still providing PrEP coverage for HPTN 083-01 participants who need it. A minor typo was also corrected in Revision 1 (Section 5.6).

2. Revisions 2, 3, and 4: NIAID DAIDS Multinational Data and Safety Monitoring Board (DSMB) and Study Monitoring Committee (SMC) references were removed. On 3 May 2022, the NIAID DAIDS Multinational Data and Safety Monitoring Board (DSMB) met to review the open and closed reports for HPTN 083-01. Given that the parent trials (HPTN 083 and HPTN 084) had been unblinded, efficacy data are now known, and CAB LA was recently FDA approved, the DSMB agreed to discontinue its reviews of the HPTN 083-01 protocol.

   Relatedly, the HPTN 083-01 Study Monitoring Committee (SMC) met approximately one month prior to DSMB meetings for this trial and had – at last meeting – decided to discontinue its reviews of HPTN 083-01, should the DSMB come to a similar decision.

Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Revision 1: Section 5.6 Step 2, Injection Phase: Safety Visits

Injection Phase Safety Visits at Week 6, 10, 18, 26, and 34

During the injection phase of the study, all participants will have brief safety visits one week after each injection. Blood will also be collected at these visits to monitor drug levels of CAB. A ~~three-month~~ supply of Tenofovir/Emtricitabine (Trade Name: TDF/FTC, Truvada®; US FDA approved generic ~~FTC/TDF~~ **TDF/FTC** comparable to Truvada® may be used) will be provided at Week 34, if the participant chooses oral follow-up (vs. CAB LA).

Revision 2: Section 6.4 Clinical Data Review

~~This study will be monitored by a NIAID Data and Safety Monitoring Board (DSMB), along with the parent protocols, which will meet at least annually to review safety and efficacy data. More frequent or ad hoc reviews of safety data may be conducted by the DSMB as needed.~~

Revision 3: Section 7.6.1 Study Monitoring Committee

~~NIAID DSMB oversight is planned for this study.~~ Monitoring guidance will be detailed in a separate Interim Monitoring Plan.
~~In addition, approximately every six months the HPTN SMC will conduct interim reviews of study progress, including rates of participant accrual, visit retention, and completion of primary and main secondary endpoint collection. The frequency and content of SMC reviews will be determined prior to the start of the study as outlined in the HPTN Manual of Procedures (MOP).~~

Revision 4: Section 10.3 Study Coordination

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and AE incidence will be monitored closely by the team ~~as well as the HPTN SMC~~.

Revision 5: Section 12.2 Appendix II. Schedule of Evaluations – Injection Phase (Step 2)

WEEKS in Study (shaded column = injection visit)	Wk 5	Wk 6	Wk 9	Wk 10	Wk 17	**Wk 18**	**Wk 25**	**Wk 26**	**Wk 33**	**Wk 34**
ADMINISTRATIVE, BEHAVIORAL, REGULATORY										
Locator information	X	X	X	X	X	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X	X	X	X	X	X
Condoms per local SOC	X	X	X	X	X	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)	X		X		X		X		X	
Qualitative interviews begin (approximately)										X
CLINICAL EVALUATIONS & PROCEDURES										
Adherence, risk reduction counseling	X	X	X	X	X	X	X	X	X	X

Medical history[1], concomitant medications, targeted physical exam	X	X	X	X	X	X	X	X	X	X
Hep B vaccination (if needed) [2]		X							X	
Blood collection	X	X	X	X	X	X	X	X	X	X
Urine collection	X	X	X	X	X	X	X	X	X	X
Rectal swab collection					X				X	
Injections for all participants	X		X		X		X		X	
ISR evaluation		X		X		X		X		X
Step 3 product choice discussion									X	X
Interviewer administered product choice assessment										X
If product chosen is oral PrEP: Provision of Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada® or US FDA approved generic) ~~(3 months' worth)~~										X
LOCAL LABORATORY EVALUATIONS & PROCEDURES										
HIV testing[3]	X	X	X	X	X	X	X	X	X	X
CBC with differential	X	X	X	X	X	X	X	X	X	X
Chemistry testing[4]	X	X	X	X	X	X	X	X	X	X
Liver function testing[5]	X	X	X	X	X	X	X	X	X	X
Fasting lipid profile[6]										X
Syphilis testing									X	
GC/CT testing (urine, rectal, and oral pharyngeal swabs)					X				X	
Urinalysis (protein, glucose; at the clinic or local lab)	X	X	X	X	X	X	X	X	X	X
Plasma storage[7]	X	X	X	X	X	X	X	X	X	X

Revision 6: Section 12.3 Appendix III. Schedule of Evaluations – Follow-up Phase (Step 3-Oral PrEP)

WEEKS SINCE LAST INJECTION	Wk +8	Wk +12	Wk +24	Wk +36	Wk +48	Early Discontinuation
ADMINISTRATIVE, BEHAVIORAL, REGULATORY						
Locator information	X	X	X	X	X	X
HIV prevention & risk reduction counseling	X	X	X	X	X	X
Condoms per local SOC	X	X	X	X	X	X
Behavioral/Acceptability assessment (CASI)		X	X	X	X	X
CLINICAL EVALUATIONS & PROCEDURES						
Qualitative interviews continue (approximately)		X	X			
Medical history[1], concomitant medications, targeted physical exam	X	X	X	X	X	X
Hep B vaccination (if needed) [2]						X
Blood collection	X	X	X	X	X	X
Urine collection			X		X	X

Rectal swab collection			X		X	
Provision of Tenofovir/Emtricitabine (Trade name: TDF/FTC, Truvada® or US FDA approved generic) ~~(3 months' worth)~~		X	X	X		
Adherence Counseling[3]		X	X	X	X[3]	X[3]
LOCAL LABORATORY EVALUATIONS & PROCEDURES						
HIV testing[4]	X	X	X	X	X	X
CBC with differential			X		X	X
Chemistry testing[5]			X		X	X
Liver function testing[6]			X		X	X
Syphilis testing			X			X
GC/CT testing (urine, rectal, and oral pharyngeal swabs)			X		X	
Urinalysis (protein, glucose; at the clinic or local lab)			X		X	X
Plasma storage[7]	X	X	X	X	X	
DBS storage		X	X		X	
HBsAb and HBcAb[8]					X	X
HCVAb					X	X

Revision 7: Appendix VII: Informed Consent for Parents/Legal Guardians and Assent for Adolescent Participants Ages 14 – Age of Majority

Permanently Stopping Study Drug

CAB pills are only given in Step 1, and then stopped permanently. If you need to leave the study before you receive any CAB injections, we'd still like to do a final study visit, which will include the same activities as the Step 3 Follow-Up Visits. If you permanently stop taking CAB after you had at least 1 CAB injection, then you will move straight to Step 3 follow-up visits, if you agree to stay in the study. In this case, ~~three months'~~ **a** supply of Truvada® (or US FDA approved generic) will be provided at Week 34.

Revision 8: Section 12.8 Appendix VIII: Informed Consent for Adolescent Participants Able to Consent for Themselves (Self-Consent) and Participants who Reach the Age of Majority

Permanently Stopping Study Drug

CAB pills are only given in Step 1, and then stopped permanently. If you need to leave the study before you receive any CAB injections, we'd still like to do a final study visit, which will include the same activities as the Step 3 Follow-Up Visits. If you permanently stop taking CAB after you had at least 1 CAB injection, then you will move straight to Step 3 follow-up visits, if you agree to stay in the study. In this case, ~~three months'~~ **a** supply of Truvada® or US FDA approved generic will be provided at Week 34.