

HIV Prevention Trials Network

Summary of Changes Included in the Full Protocol Amendment of HPTN 084

DAIDS Document ID # 38070

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

The Amended Protocol is identified as:

Version 2.0, dated 6 November 2019

Information for Investigators

The modifications included in this protocol amendment and the associated rationale are summarized briefly below. HPTN 084 study investigators will submit this Summary of Changes and the corresponding protocol Version 2.0 and informed consents to all relevant regulatory authorities and Institutional Review Boards/Ethics Committees (IRBs/ECs) for approval. Upon receipt of all IRB/EC approvals, sites should begin implementation of the amended protocol immediately. The site will submit all required documents to DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center.

This Amendment and all related IRB/EC correspondence must be retained in the site regulatory file in other pertinent files.

RATIONALE

The version 1.0 protocol of 2 March 2017 is being updated to target women at higher risk of HIV acquisition. The version 1.0 protocol permitted enrollment of women who scored >2 using a modified Voice Risk Score (VRS). One eligibility criterion is being revised to now only allow women with a modified VRS of ≥ 5 to enroll. In addition to this change, the protocol amendment more clearly spells out both the Contraceptive and Qualitative sub-studies. Finally, this full amendment incorporates three Letters of Amendment (LoAs) and three Clarification Memos (CMs).

Summary of Revisions and Rationale

General Updates:

- The protocol is being updated to incorporate LoA #1, LoA #2, LoA #3, CM #1, CM #2 and CM #3 (please note that the revisions and rationales affiliated with all LoAs and CMs are not included in this summary, as they are outlined in each previously approved LoA and CM).
- The protocol is updated throughout for minor editorial changes and typographical errors.

List of Abbreviations and Acronyms:

- Five additional acronyms were added to provide context for commonly used acronyms used throughout the protocol.

Protocol Team Roster:

- David Burns was removed from the protocol team roster.
- Laura McKinstry was removed from the protocol team roster.
- Heather Nobel and Kimberly Scarsi were added to the roster as protocol team members.
- Mina Hosseinipour and Mark Marzinke's titles were updated.
- Katie Shin's fax number was updated.

Schema:

- Language in each step was edited from "provision of condoms" to "offer of condoms."
- The number of endpoints needed to complete Step 2 was increased from 111 to 114.
- A tertiary objective was added to compare any differences in weight gain and BMI.
- A tertiary objective was modified to include measurement of etonogestrel.
- The tertiary objective to determine luteinizing hormone, follicular stimulating hormone and progesterone concentrations in participants receiving DMPA or NET-EN was removed.

Overview of Study Design Figure:

- Language was modified from "provision of condoms" to "offer of condoms."

1.2 Overview of Oral CAB and CAB LA

- Revised to include current version of the CAB Investigator's Brochure (IB).

1.5.1 Oral CAB

- Revised to include current version of the CAB IB.

1.5.2 CAB LA

- Revised to update the current status and results from HPTN 077.
- Added text from data gathered post version 1.0 confirming the dosing regimen for 600 mg of CAB LA.

1.5.3 Genital Tract (GT) Tissue Concentrations after Oral and Injectable Administration

- This section was relocated to 1.5.3.

1.6 Clinical Experience to Date: Oral CAB and CAB LA

- This section was revised to include more recent data.
- Table 1.3 was updated and relocated to this section.

1.7 Pregnancy and Pregnancy Prevention with CAB Use

- Results from HPTN 077 were added.
- The following sentence, which was updated in CM#2, was deleted: “This study will permit characterization of the pharmacokinetics of injectable contraceptives during concomitant CAB LA administration in a subset of study participants.”

1.9 Weight Gain

- This section was added to provide evidence and background for including the tertiary objective of comparing weight gain, by arm.

2.3 Tertiary Objectives

- Revisions, previously described, were made.

2.4 Study Design and Overview

- Revisions, previously described, regarding offer of condoms were made.
- Clarification of participant management in cases of premature study product discontinuation were added.
- Details were added to better describe both the Contraceptive and Qualitative sub-studies.

3.1 Inclusion Criteria

- The modified VRS was increased from greater than 2 to greater than or equal to 5.
- Additional language was added to clarify the creatine clearance inclusion criterion.
- Added a sentence clarifying the procedure for any participant with a positive HIV test result at enrollment.

3.2 Exclusion criteria

- IMPAACT 2026 was included as an exception to co-enrollment exclusion criteria.
- Current or past enrollment in an HIV broadly neutralizing antibody trial was added as an exclusion criterion.

3.4 Co-Enrollment Guidelines

- A description of participants that are able to co-enroll in IMPAACT 2026 was added.

3.6 Participant Withdrawal

- Clarification was added to provide guidance on participant management for participants who decline study product.

4.1 Study Product Regimens/Administration/Formulation Content

- Minor wording updates were made to make the text consistent with HPTN 083.

4.1.1 Oral Product

- Updates were made to study product descriptions and handling instructions.
- Minor updates were made to make the text consistent with HPTN 083.

4.1.2 Injectable Suspension

- Updates were made to study product descriptions and handling instructions in the first paragraph. These updates were initially made in CM#3.
- Minor updates were made to make the text consistent with HPTN 083.

4.2 Study Product Preparation

- This is a new section. The text is consistent with text in HPTN 083.
- Detailed instruction on both oral and injectable study product preparation were added.

4.3 Study Product Acquisition and Accountability

- This section was re-numbered from “4.2” to “4.3” to accommodate the new Section 4.2.
- Text was updated to make it consistent with HPTN 083.

4.3.1 Study Product Acquisition

- Added etonogestrel implants.

4.3.2 Study Product Accountability

- Text was added to be consistent with HPTN 083.

4.4 Other Study Product Dispensing Considerations

- This is a new section. The text is consistent with text in HPTN 083.

4.5 Toxicity Management

- This section was re-numbered from “4.3” to “4.5” to accommodate the new Sections 4.2 and 4.4.

4.6 Concomitant, Prohibited, and Precautionary Medications

- This section was re-numbered from “4.4” to “4.6” to accommodate the new Sections 4.2 and 4.4.
- Deleted instruction to reference the SSP for the list of prohibited medications.
- Added instruction and list of prohibited medications.

5.2 Step 1, Oral Run-in Phase: Enrollment

- Revised to reflect changes made to the Contraceptive Sub-Study.

5.3 Step 1, Oral Run-in Phase: Safety Visits

- Clarified that adequate product exposure is required to move into Step 2.

5.3.1 Management of Participants with AEs during Step 1

- Table 5.1 text was revised to make it more reader friendly.

5.4 Step 2, Injection Phase: Injection Visits

- A sentence was added to clarify that the first study product injection is given at the Week 5 visit.
- Added instructors for contacting the CMC when a participant misses an injection.
- Updated the information about the Contraceptive Sub-Study.

5.7.2 Adherence Counseling and Monitoring

- A note was added clarifying there are no minimal oral adherence requirements in Steps 2 or 3.

5.8 Injection Visit Windows

- Text describing visit windows was added.

5.9 Procedures for Continued Oral and Injectable Dosing

- A sentence was added to consult Section 5.4 for temporary study product hold instruction.

5.10 Procedures for Participants n Step 2 Who Do Not Complete the Full Course of Study Product

- Minor clarifications to the outlined procedures were added.

5.11.2 After Study Enrollment/Randomization

- Edits from LOA#2 were incorporated. Guidance for management of any seroconverters in Step 3 will be given by members of the HIV alias group.

5.14 Pregnancy

- Additional detail was added to revisions made in Letter of Amendment #3.

5.15 Participants who decline to use long acting contraception

- The Section title was changed from “Participants who discontinue long acting contraception” to “Participants who decline to use long acting contraception.”
- Additional detail was added to revisions made in Letter of Amendment #3.

5.16 Acceptability Assessments

- This section was updated to include the Qualitative Sub-Study.

5.17 Interim Contacts and Visits

- A note regarding HIV testing at interim visits was added for clarification.

6.0 Safety Monitoring and AE Reporting

- Minor text revisions were made throughout to improve readability.
- Weblinks were updated.

7.1 Review of Study Design

- Updated the number of endpoints.

7.2.2 Primary Safety Endpoint

- Edited the Primary Safety Endpoint; moved criteria from Grade 3 to Grade 2 or higher clinical and laboratory AEs.

7.2.3 Secondary Endpoints

- The Section title was changed from “Secondary Efficacy Endpoints” to “Secondary Endpoints.”
- Secondary Endpoints were revised to directly correlate with Secondary Objectives.

7.2.4 Tertiary Endpoints

- Tertiary Endpoints were revised to directly correlate with Tertiary Objectives.

7.3 Sample Size and Interim Monitoring

- Revised to update the targeted number of events/endpoints.
- Tables 7.2, 7.3 and an explanation were added.

7.8.2 Analyses of Primary Safety Objective

- Grade 3 AE was changed to Grade 2.

7.8.4.2 Measurement of Adherence

- The TFV level was erroneously changed to 35.5ng/mL in CM#2. The value was corrected during version 2.0 editing.

7.8.5.1 Qualitative Analysis

- Revised to reflect the updated aims of the qualitative analysis.
- Updated text from “NVivo 11” to “NVivo12.”

7.8.6 Analyses of Tertiary Objectives

- Planned analyses were updated to reflect the changes in tertiary objects.

9.1 Local Laboratory Specimens

- Minor clarifying text edits were made.

9.2.1 Virology

- Clarification that HSV-2 testing will be performed on stored plasma.

9.2.2 Pharmacology

- A note that central lab staff may be unblinded, and under what circumstances, was added.
- A description of samples that are needed for the Contraceptive Sub-study was added.

9.3.5 Specimen Storage and Possible Future Research Testing

- This section of the protocol was numbered as 9.3.5.

11.0 References

- References with new information important to the protocol were added.

10.4 Study Monitoring

- Updated the list of entities permitted inspection access to study-related documents on site.

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

- Revisions to the table were made to incorporate the updated Objective for weight.
- Footnotes were updated to provide clarification of some study procedures.

Appendix Ib. Schedule of Evaluations -Step 2, Injection Phase

- Revisions to the table were made to incorporate the updated Objective for weight.
- Footnotes were updated to provide clarification of some study procedures.

Appendix Ic. Schedule of Evaluations -Step 3, Follow-up Phase

- Revisions to the table were made to incorporate the updated Objective for weight.
- Footnotes were updated to provide clarification of some study procedures.

Appendix Id. Schedule of Evaluations for Pregnant Participants

- Revisions to the table were made to incorporate the updated Objective for weight.
- Footnotes were updated to provide clarification of some study procedures.
- Revisions to the schedule of events from LOA#3 were made. STI testing will be done at baseline and every six months thereafter. Also, a medical history and targeted medical exam will be conducted at the baseline visit.

Appendix Ie. Schedule of Evaluations – Contraceptive Sub-Study

- This appendix was added to provide details for the evaluations in the Contraceptive Sub-Study.

Appendix II. Schedule of Evaluations -Step 2, Injection Phase

- Revisions to the table were made to incorporate the updated Objective for weight.
- Footnotes were updated to provide clarification of some study procedures.

Appendix III. Toxicity Management

- Revised to include clarifications for creatinine clearance and CPK.
- Clarifying text was added for product discontinuation.
- For participants in Step 2 who discontinue product, text was revised to include annual HIV testing until the end of Step 3.
- Instructions were added to contact the CMC for further guidance on investigation and study product administration.
- Additional details for managing participants with creatinine clearance issues were included.

Appendix IV: Sample Screening and Enrollment Informed Consent Form

- LOA#3 was incorporated into the consent form. LOA3# requires all participants be on a long-acting contraception method and that participants provide documentation.
- Revisions were made to include further detail on the Contraceptive and Qualitative Sub-Studies.
- Text was added that indicates that participants who do not complete the full course of study product will be followed at least annually for HIV testing until Step 2 and 3 follow-up is complete.

- Text clarifying that additional blood will be needed for management if a participant tests positive for HIV.
- A section was added to describe possible injection side effects.
- Text with the most up to date information on dolutegravir was added.
- Text explaining procedures in the event of a pregnancy was updated.
- Text noting that the study will not pay for a fetal ultrasound was added.

Appendix V: Sample Qualitative Informed Consent Form

- The General Overview and text throughout were updated quite a bit to be more informative.
- Focus Groups were removed from the consent form, since no focus group discussions will be conducted.
- The following sentence was removed: “The recording will be destroyed after the study.”