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 5.0 dated 6 October 2023

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 5.0 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 4.0 protocol of 2 Nov 2022 is being updated to extend CAB LA access for two additional injections (approximately 16 additional weeks) for participants wishing to continue maintenance dosing of CAB LA and who live in locations where CAB LA is not yet otherwise available. Only a subset of participants will be eligible for two additional injections. This amendment also includes updated CAB LA risk language, reflecting the current IB, and the HIV algorithm has been moved to the protocol. Previously the HIV algorithms were only in the SSP; now they are in both places. This full amendment also incorporates Clarification Memo #1 to the v4.0 protocol.

Summary of Revisions

- The protocol is being updated to incorporate CM #1 (please note that the revisions and rationale affiliated with CM#1 are not included in this summary, as they are outlined in the previously approved CM).
- The protocol is updated throughout for minor editorial changes to improve flow/readability and correct typographical errors.

Changes to the Protocol Roster

- Updated room numbers for Katherine Shin and Lydia Soto-Torres

Throughout the V5.0 Protocol/ Appendix VIII: Procedures for Offering Open Label (OL) Cabotegravir-

- The v5.0 protocol amendment makes two changes of significance:
    - 1) it extends CAB LA access for two additional injections (approximately 16 additional weeks) for participants wishing to continue maintenance dosing of CAB LA and who live in locations where CAB LA is not yet otherwise available.
    - 2) CAB LA risk language has been updated to reflect the current Investigator's Brochure (IB) (IB version 13, dated 31 Jan 2023).
- Throughout removed text related to Steps 4a & 4b as all participants are past those Steps.

Section 2.0 (Purpose and Overview)

- Under sub-section 'OL2 of the Study' added references to 45 CFR 46, Sub-Parts B and D.

Section 2.3 (Special Considerations)

- Removed text "Drug metabolism may be altered during pregnancy." This is an editorial change. The rest of the paragraph describes how drug metabolism is altered in pregnancy.

Section 3 (Description of Steps 4, 5 and 6 during the V5.0 Protocol)

- Added to Step 4d- bullet 'who were Exposed to CAB LA" to clarify Step 4d is only for those who have had at least one dose of CAB LA.
- Added the note to the Step 6 bullet:
    - * NOTE: Participants who reach Week 96 on maintenance doses of CAB LA and wish to continue using CAB LA but where local access is delayed for any reason will be offered two additional doses (approximately 16 weeks) on Step 6. These participants will have visits at Weeks 104 and 112.

Section 3.1 (Overview of Steps 4d, 5 and 6

- Clarified that in the OLE, participants had up until week 24 visit to choose to start CAB LA. Some participants may have chosen to start CAB LA during their pregnancy. All participants who wish to take CAB LA during pregnancy are required to consent for Step 4d. Participants in Step 4d who choose to use OL TDF/FTC during pregnancy may re-start CAB LA in the post-partum period following consultation with the CMC. Additional safety assessments and PK samples will be collected at study visits four weeks after every injection.
- Listed out the additional local laboratory tests and procedures required for Step 4d. Nothing changed here. What is the in SOE for Step 4d is just repeated here.

- Corrected how long SAEs, including deaths and congenital anomalies will be reported throughout the post-partum period. Previous text said 12 month and it has been corrected to 11-month post- partum period (48 weeks).
- Clarified that procedures for sample processing, testing and storage are provided in the SSP Manual. Assessments using stored samples from the Pregnancy and Infant Sub-Study will not be returned to study sites or participants.
- Clarified what happens to pregnant participants who received at least one CAB injection but who decline participation in Step 4d (Pregnancy and infant stub-study) and are followed in Step 5. They will be asked to consent to provide updates on any SAEs as well as to consent to live infant assessment of growth parameters at delivery and 48 weeks post-delivery. This is not a change; text adds a further explanation. Also added that site staff will refer pregnant participants for pregnancy care and an ultrasound.
- Under the Step 6 header, corrected the number of visits within 48 week follow-up. Participants will be followed for 48 weeks on CAB LA at visits every eight weeks for a total of seven (not six) visits.

Step 4c, Appendix VIII: Schedule of Evaluations for Step 4c- Procedures for Participants on Maintenance Doses of CAB LA or TDF/FTC

- Added text to footnote (1): For participants who are pregnant and on Step 4c, site staff will refer participants to pregnancy care outside of the study. Ideally an ultrasound will be conducted by Week 12 of the pregnancy. Site staff will report the ultrasound findings into the database. Site staff will also collect SAEs and conduct infant assessments at both delivery and at 48 weeks post-delivery and report those data. All infant SAEs that occur up to 48 weeks post-delivery will be reported.

Step 4d, Appendix VIII: Schedule of Evaluations for Step 4d- Procedures for Pregnant/Breastfeeding Participants who were Exposed to CAB LA, and Their Infants

- Added Infant AE assessments at Weeks 32, 40 and 48 post-partum.
- Added a clarification to first note in SOE that PK analysis will be performed at a laboratory designated by the HPTN LC (vs it used to just say 'an offsite laboratory').
- Added urine collection to Week 36 visit.

Step 5: Appendix VIII: Schedule of Evaluations for Step 5- Procedures for Participants Taking OL TDF/FTC for 48 Weeks after Premature CAB LA Discontinuation

- Added text to footnote (5): For participants who are pregnant and on Step 5, site staff will refer participants to pregnancy care outside of the study. Ideally an ultrasound will be conducted by Week 12 of the pregnancy. Site staff will report the ultrasound findings into the database. Site staff will also collect SAEs and conduct infant assessments at both delivery and at 48 weeks post-delivery and report those data. All infant SAEs that occur up to 48 weeks post-delivery will be reported.

Step 6: Appendix VIII: Schedule of Evaluations for Step 6-Procedures for Participants on Maintenance Doses of CAB LA weeks 49-96 (or Weeks 49-112)

- Added weeks 104 and 112 to SOE. Also note that the behavioral assessment is at week 104 and the acceptability assessment is at week 112.
- Added cholesterol to footnote 6.
- Added two footnotes:

  # At Week 96, site staff must determine whether the PPT can access CAB LA locally, outside of the trial. If the PPT has access to CAB LA, Week 96 will be the final visit. If local access to CAB LA is delayed for any reason, offer the PPT up to two additional injections on the study (Weeks 104 and 112).

  - $ At Week 104 of Step 6, if a PPT has not already been reconsented for Week 104 and 112 visits, she must be consented.

Section 3.2 (Overview of Managing Participants with HIV Reactive Tests)

- Added HIV Testing Algorithm to be Followed During Steps 4-6.

Section A. Information in the Main Protocol that is Not Relevant to Protocol, V5.0

- Clarified that sites should follow Appendix III for Section 9 instructions.

Section 4.0 (Modified from the Main Protocol)

- Added that CAB was approved by the US FDA for the prevention of HIV-1 infection in December 2021.

Section 5.10 (Procedures for Participants in Steps 4c, 4d, or 6 who do not complete the full course of study product.

- Added a note about Premature Discontinuation for Step 4d.

Section 5.14 Pregnancy

- Added clarification note that regardless of the Step a pregnant participant is followed on, first trimester ultrasound findings and pregnancy outcome data (infant growth assessment at delivery and approximately 48 weeks post birth) will be collected. All infant SAEs that occur up to 48 weeks post-delivery will be collected and reported.

Section 7.0 (Modified from the Main Protocol)

- Minor clarifications were made to the statistical analysis section.

Section 9.0 (Modified from the Main Protocol)

- Added this section.

Toxicity Management

- Removed first sentence under Grade 4 as it relates to AEs prior to first injection. That is no longer relevant.
- Guidance on Toxicity management for Specified Toxicities (Elevations in ALT)
    - Removed text for Oral CAB (Step 4a). Step is no longer relevant.
    - Removed sentence for TDF/FTC (Step 4c) as it is covered in the section below this text.

Addendum to the Sample Informed Consent

- All new information is highlighted in gray so the participant can more easily see what new information has been added.
- Editorial changes throughout the consent to improve flow/readability.
- CAB LA study product (oral and LA injectable) was approved by the US FDA for the prevention of HIV-1 injection in December 2021.
- Added that urine may also be collected to the bullets that mentions chlamydia, gonorrhea and trichomonas testing.
- Updated the weeks where injection locations will be checked.
- Minor corrections to the clinicaltrials.gov language.
- Removed language to Steps 4a and 4b as participants are past these steps.
- Updated side effects to be in alignment with the updated IB version (version 13, dated 31 Jan 2023).
- Added text about why two additional CAB LA injections are being offered to participants.
- Added text around what will happen at the Week 96 and 112 visits.
- Added text pertaining to women who become pregnant and have only ever taken TDF/FTC or for women who do not want to do the additional study visits.