

Clarification Memo # 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 1.0, dated 2 March 2017

Final Clarification Memo (CM) Version: Final of 26Sep2017

Summary of Revisions and Rationale

1. The Protocol Team Roster has been updated to reflect a change in study pharmacists and lab staff.
 2. Wording of the first Tertiary Objective has been clarified.
 3. Updated DAIDS Toxicity Tables reference to incorporate the Corrected Version 2.1, July 2017 guidelines.
 4. Typographical errors have been corrected in the protocol. No change in procedures or implementation was made.
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Implementation

The procedures clarified in this memorandum have been approved by the Division of AIDS (DAIDS) Medical Officer and are to be implemented immediately upon issuance. IRB approval of HPTN 084 Protocol Clarification Memo (CM) #2 to HPTN 084, Version 1.0 is not required by the sponsor; however, sites may submit the CM to the responsible IRBs for their information.

No change in the informed consent forms is necessitated by or included in this CM, aside from the corrected typographical errors.

The modifications included in this CM will be incorporated into the next full protocol amendment. Text noted below by ~~striketrough~~ will be deleted; text appearing below in **bold** will be added.

Revision 1-Related Changes: Edited Protocol Roster to Reflect Pharmacy and Lab Staff Change

Revision 1, Change 1) Replaced B Patel with K Shin in the Protocol Roster, pages 12 and 13

Katherine Shin, Pharm. D.
Senior Pharmacist
Pharmaceutical Affairs Branch
Division of AIDS
5601 Fishers Lane
Room 9D30A, MSC 9829
Bethesda, MD 20892-9829
United States
Phone: 240-627-3047
Fax: 240-627-3112
E-mail: KaShin@niaid.nih.gov

~~**Bijal Patel, Pharm. D., BCPS [c]**~~
~~Pharmacist~~
~~Pharmaceutical Affairs Branch~~
~~OCSO, DAIDS, NIAID, NIH~~
~~5601 Fishers Lane~~
~~Room 9A19~~
~~Rockville, MD 20852~~
~~United States~~
~~Phone: 240-669-5404~~
~~Fax: 240-627-3112~~
~~E-mail: Bijal.patel@nih.gov~~

Revision 1, Change 2) Removed P Richardson from Protocol Roster, page 12

~~**Paul Richardson, MSc**~~
~~HPTN Laboratory Center Senior QA/QC Coordinator~~
~~Johns Hopkins University~~
~~Department of Pathology~~
~~Pathology Building 306~~
~~600 N. Wolfe St.~~
~~Baltimore, MD 21287~~
~~United States~~
~~Phone: 410-502-0435~~
~~Fax: 410-614-0430~~
~~Email: pricha18@jhmi.edu~~

Revision 2-Related Changes: Clarified text in a Tertiary Objective

Revision 2, Change 1) Edited text in Section “Schema” on page 19, in Section 2.3, “Tertiary Objectives” on page 40 and in Section 7.8.6, “Analyses of Tertiary Objectives” on page 77

“To estimate ~~and compare~~ sexual risk behaviors, as measured by self-report and rates of incident sexually transmitted infections (STIs), ~~between study arms.~~”

Revision 3-Related Changes: Updated Protocol Text to Incorporate New DAIDS Toxicity Tables of July, 2017

Revision 3, Change 1) Edited text in Section 6.1, “Definition and Reporting” Section on page 62

“AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, **Corrected** Version 2.01, ~~November 2014~~ **March July 2017**. This version will be used for the entire duration of the study.”

Revision 3, Change 2) Edited text in Section 6.2.3, “Grading Severity of Events” Section on page 63

“The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected** Version 2.01, ~~November 2014~~ **March July 2017**, will be used for the entire duration of the study for determining and reporting the severity of AEs. The DAIDS grading table is available on the DAIDS RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

Revision 4-Related Changes: Clarifications and Typographical Errors Corrected in the Protocol

Revision 4, Change 1) Edited text in Protocol Roster to correct typing error on page 10

“Yaw Agyei, MPH, BS (MT)
HPTN Laboratory Center
Johns Hopkins University
Department of Pathology”

Revision 4, Change 2) Edited text in Protocol Roster to incorporate professional title on page 11

“Craig W. Hendrix, MD
HPTN LC Protocol Pharmacologist
Director, Clinical Pharmacology
Johns Hopkins University”

Revision 4, Change 3) Added clarification of X-axis values for Figure 1.4 on page 32

“>1x above PAIC₉₀ >4x above PAIC₉₀ >8x above PAIC₉₀”

Revision 4, Change 4) Edited text in Section 1.7, “Pregnancy and Pregnancy Prevention with CAB Use” on page 37

“This study will permit characterization of the pharmacokinetics of injectable contraceptives during concomitant CAB LA administration **in a subset of study participants.**”

Revision 4, Change 5) Corrected VOICE score in Section 3.1, “Inclusion Criteria” by removing the “equals” sign on page 44

“Score of \geq 2 using a modified risk score.”

Revision 4, Change 6) Edited text in Section 4.2.1, “Study Product Acquisition” on page 50

“DMPA and/or NET-EN will ~~be~~ not be provided by the Study Sponsor.”

Revision 4, Change 7) Edited text of Section 5.2, “Step 1, Oral Run-in Phase: Enrollment” on page 52

“Subjects currently taking injectable contraceptives and opting to participate in the contraceptive sub-study (**up to 100 evaluable participants**) should have ~~PK~~ **blood for pharmacological analysis** and”

Revision 4, Change 8) Edited text of Section 5.13, “HBV and HCV” on page 59

“Testing for HBV and HCV will be performed at Screening (HBsAg and HCAb). Persons positive for these tests will not be enrolled in the study and will be referred to their primary provider for management. Persons with a positive HCV Ab test at Screening will be excluded from the study, ~~even if HCV RNA is undetectable. At Enrollment, p~~ **Participants will be tested for Hepatitis B surface antibody (HBsAb), and Hepatitis B core antibody (HBcAb, total).** Participants who do not have evidence of immunity to HBV (e.g., negative HBsAb) will be provided HBV vaccination. For participants who do not have evidence of HBV immunity at Enrollment, HBV testing should be repeated at the discretion of the IoR or designee during the study if clinically indicated, if the participant has elevated AST/ALT results (elevated level at discretion of IoR or designee), or if the participant expresses a concern about having acquired HBV infection after enrollment. Refer to the SSP Manual for persons who have a positive result for HBcAb **(total)** only.”

Revision 4, Change 9) Edited Section 7.2.3, “Secondary Efficacy Endpoints” on page 66

“~~Secondary Endpoints~~ **Efficacy Endpoints**”

- “Number of documented incident HIV infections in participants in subgroups broken down by baseline age, HSV-2 status, contraceptive use method and BMI \leq/\geq 25 kg/m²
- Plasma ~~and DBS~~ levels of CAB in participants randomized to CAB/CAB LA
- Plasma **and DBS** levels of TFV/TFV-DP in participants randomized to TDF/FTC
- Survey of attitudes and willingness to use CAB LA and TDF/FTC”

Revision 4, Change 10) Edited text in Section 7.8.4, “Considerations for a Supportive Analysis if Adherence to TDF/FTC is Higher than Expected” on page 71

“In the following **sections** we outline the rationale and develop the methods for a supportive adherence-dependent NI comparison of injectable CAB LA to daily oral TDF/FTC.”

Revision 4, Change 11) Edited text in Section 7.8.4.2, “Measurement of Adherence” on page 74

“In HPTN 084, adherence will be measured at a subset of study visits in a random sample of 400 participants **enrolled into Arm B**. A participant will be defined as adherent at a given visit if her plasma TFV level is greater than ~~0.34~~ **35.5** ng/ml. Given the average of 2.6 years of follow-up, this sampling plan should yield up to ~~1,6003,200~~ samples for analysis, distributed proportionately across the follow-up period. Based on this sample size, the estimate of adherence for the study cohort should have a precision (width of a 95% confidence interval) of between ± 0.05 and ± 0.0167 (depending on the magnitude of the intra-class correlation between repeated samples on the same participant).”

Revision 4, Change 12) Edited text in Section 7.8.5, “Analyses of Secondary Objectives” on page 77

“The team will also investigate using a model to predict drug levels in continuous time based on observed plasma and ~~PBMC~~ **DBS** levels; the predicted values could then be used as a covariate in the analysis proposed here. Potential confounders (e.g. age, sexual risk behaviors) will be included in the model.”

Revision 4, Change 13) Edited text in Section 9.1, “Local Laboratory Specimens” on page 82

“Chemistry testing (blood-urea nitrogen (BUN) **or** urea, creatinine, CPK, glucose, calcium, phosphorous, amylase, lipase).”

Revision 4, Change 14) Edited text in Section 9.2, “Stored Specimens, Injectable Contraception Sub-Study” on page 83

“NOTE: Samples may be unblinded at the HPTN Laboratory Center (Pharmacology Laboratory only), so the relevant assays are only performed on participants who received CAB LA. In any such case, no one outside the Pharmacology Laboratory will be unblinded prior to the end of the trial (see Section 5.17).”

Revision 4, Change 15) Edited text in Section 9.3.1, “QC for HIV Diagnostic Testing” on page 84

“Throughout the course of the study, the **sites will ship an aliquot per visit per participant quarterly. The HPTN LC with guidance from the SDMC HPTN LC** will select a random sample of stored specimens to test for QA purposes. The total number of specimens undergoing QA testing will follow the QA processes as described in the HPTN MOP and at the discretion of the HPTN LC.

~~The HPTN LC will inform site staff of the samples selected for QA testing, and site staff will ship the selected specimens to the HPTN LC.~~

Revision 4, Change 16) Edited text in Section 9.3.4, “Quality Assurance for HIV RNA Testing” on page 85

“Local laboratories may also perform HIV RNA/viral load testing (**test kit approved by the HPTN LC**) as indicated in Appendix II or for evaluation of possible acute HIV infection.”

“Samples from participants who did not successfully enroll in the study may be discarded **once** sample lists are provided by the HPTN SDMC in consultation with the HPTN LC.”

Revision 4, Change 17) Removed “12” and the footnote it refers to from Appendix Ia “Schedule of Evaluations – Screening and Step 1, Oral Run-in Phase” on page 94

“DBS storage¹²”

~~“¹²For Arm B (TDF/FTC) participants only.”~~

Revision 4, Change 18) Changed footnote “13” to footnote “12” on page 94

“Additional sample storage for participants enrolled in the Injectable Contraception Sub-Study¹³¹²”

Revision 4, Change 19) Edited text in “FOOTNOTES FOR APPENDIX Ia” on page 94

“⁷ At Screening: HBsAg and HCV antibody testing. At Enrollment: HBsAb and HBcAb testing. **Note: These tests can all be done at Screening at the discretion of the IOR.**”

“¹⁰ Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. **If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.**”

Revision 4, Change 20) Edited text in Appendix Ib “Schedule of Evaluations –Step 2, Injection Phase” on pages 95 and 96

“Adherence counseling ~~for Arm B~~”

“DBS storage¹⁰”

~~“¹⁰For Arm B (TDF/FTC) participants only.”~~

Revision 4, Change 21) Edited text in “FOOTNOTES FOR APPENDIX Ib” on page 96

“⁷ Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. **If participants are not fasting, do not order the lipid testing. Participants may return for testing or it can be performed at next visit.**”

Revision 4, Change 22) Edited text in “FOOTNOTES FOR APPENDIX Ic” on page 97 and as a consequence, renumbered footnote numbers for APPENDIX Ic and the remaining footnotes on pages 97 and 98

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

Time in Step 3	Step 3, Day 0*	Step 3, Week 12	Step 3, Week 24	Step 3, Week 36	Step 3, Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator information	X	X	X	X	X
HIV prevention counseling	X	X	X	X	X
Offer condoms	X	X	X	X	X
Acceptability assessment [†]	X				
Behavioral assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
CLINICAL EVALUATIONS & PROCEDURES					
Dispense pills to all participants	X	X	X	X	
Adherence counseling for all participants	X	X	X	X	
Review ISR Memory Aid	X				
Medical history, concomitant medications, contraceptive use, targeted physical exam	X	X	X	X	X
Blood collection	X	X	X	X	X
Urine collection	X ⁷⁶	X ⁴³	X	X ⁴³	X
Vaginal swab collection ²¹	X ⁷⁶		X		X
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing ²²	X	X	X	X	X
Pregnancy testing ⁴³	X	X	X	X	X
Chemistry testing ⁵⁴			X		X
Liver function testing ⁶⁵			X		X
Syphilis testing	X ⁷⁶		X		X
GC/CT and TV testing ²¹	X ⁷⁶		X		X
Plasma storage ⁸⁷	X	X	X	X	X
DBS storage			X		X

FOOTNOTES FOR APPENDIX Ic

* Day 0 of Step 3 should be scheduled no later than 8 weeks after the last injection. Attempts should be made to bring the participant in earlier rather than later than the target date. See SSP Manual for further details.

[†] Administer Acceptability Assessment at week 0 as final assessment if not done in the previous 24 weeks on step 2, to include a brief preference assessment.

²¹ GC/CT NAAT testing may be performed using urine or a vaginal swab; TV testing is performed using a vaginal swab.

³² The HIV testing algorithm is provided in the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory. At least one HIV test must be available the same day as sample collection and before product is administered.

⁴³ Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Results must be available the same day as sample collection and before product is administered. Testing may be

performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Pregnancy testing is not required at subsequent visits if a positive result is obtained and the pregnancy is still ongoing.

⁵⁴ Chemistry testing includes: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

⁶⁵ Liver function testing includes: AST, ALT, TBili, and alkaline phosphatase.

⁷⁶ Skip Day 0 if testing has occurred within the last 3 months of Day 0, and do only at Weeks 24 and 48.

⁸⁷ Stored plasma will be used for Quality Assurance testing and other assessments at the HPTN LC (see Section 9). Assessments will be performed retrospectively; results will not be returned to study sites or participants, except as noted in Section 9.0.

Revision 4, Change 23) Edited text in Appendix IV: Sample Screening and Enrollment Informed Consent Form, within the section titled “Step 2: CAB LA Injection or TDF/FTC Dispensing Visit Activities” on page 116

“These visits will last up to XX hours. During these visits, ~~7~~ in addition to the activities...”

Revision 4, Change 24) Removed redundant sentence from text in Appendix IV: Sample Screening and Enrollment Informed Consent Form, within the section titled “Pregnancy” on page 122

“If you wish to be pregnant in the next few years, you should not participate in this research study. We do not yet know how CAB LA might affect a baby during pregnancy. We would like you to be cautious about falling pregnant. There are few data from humans on the effects of CAB in pregnancy. Most of the information we have comes from animal studies. ~~Birth defects have not been observed in animal studies with CAB, to date.~~ In studies done in pregnant rats and their newborns, using very high amounts of CAB, there were more baby rats that died when they were born or right after they were born. This did not happen to the baby rats when the mother got lower amounts of the drug, or no drug. The amount of CAB that we are giving in this study is expected to be more than 7-times lower than the amount given to the pregnant rats. Birth defects have not been found in any animal studies of CAB so far. We do not know whether what happened to the baby rats has any impact on what will happen in pregnant humans taking this drug. That is why if you are female and participating in this study, you cannot be pregnant, and we want you to take birth control the entire time you are in the study and also for a year after.”