

FINAL
SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:
HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV Uninfected Cisgender Men and Transgender Women who have Sex with Men, Version 2.0, July 25, 2018

DAIDS Document ID: 20725

THE AMENDED PROTOCOL IS IDENTIFIED AS:

Final Version 3.0
October 31, 2019

IND #122,744

Information/Instructions to the Study Sites from the Division of AIDS

The information contained in this protocol amendment impacts the HPTN 083 study and must be submitted to site Institutional Review Boards and/or Ethics Committees (IRBs/ECs) as required as soon as possible for review and approval. This amendment impacts the study informed consent form (ICF); all study sites must prepare updated informed consent forms and obtain IRB/EC approval of the updated forms. Approval also must be obtained from other 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 obtaining all required IRB/EC approvals and any other applicable regulatory entity approvals, each site should immediately begin implementing this amendment, using site-specific Version 3.0 ICFs when obtaining informed consent under protocol Version 3.0. Re-consent for specimen storage and future research, genetic testing, and the DXA subset (where applicable) is not required.

Upon receiving IRB/EC approvals and any other applicable regulatory entity approvals, all sites are required to submit an amendment registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center. Sites will then receive a registration notification for the amendment after the DAIDS PRO verifies that all required registration documents have been received and are complete. Sites should not await this notification before implementing this amendment.

This Summary of Changes, Protocol Version 3.0, corresponding site-specific informed consent forms, and all associated IRB/EC and regulatory entity correspondence should be retained in each site's essential document files for HPTN 083.

The Division of AIDS Regulatory Affairs Branch will submit this amendment to the United States Food and Drug Administration (FDA) for inclusion in Investigational New Drug application (IND) #122,744.

Summary of Revisions and Rationale

The modifications included in this protocol amendment and the rationale are summarized below and detailed in the ‘implementation’ section that follows. The modifications are presented generally in order of their appearance in the study protocol. The major items included in this protocol amendment are as follows:

1. The protocol title page and protocol signature page are updated for Version 3.0.
See Revisions 1 and 2.
2. The Protocol Team Roster contact information is updated for Tim Holtz. Andrea Jennings is added as a protocol team member, and David Burns is removed.
See Revision 3.
3. Two substantive changes are included in this amendment per a recommendation from the HPTN 083 Study Monitoring Committee, which met via teleconference on April 12, 2019, and was subsequently endorsed by the NIAID Multinational Data and Safety Monitoring Board at their meeting held on May 9, 2019. The recommendations are related to concerns about overall low HIV incidence in the study, and the modifications related to these two recommendations included in this amendment are 1) increasing the overall N of the study from approximately 4500 to 5000, where specific sites in areas of higher viral burden will then enroll an additional 500 participants; and 2) capping the duration of follow-up at sites such that each individual participant will be followed for approximately 4 years, with 3 years on blinded study product, followed by one year of open-label daily oral TDF/FTC. Several protocol sections are impacted by these changes, including the addition of a new Section 5.8: Schema, Overview of Study Design and Randomization Scheme, 2.5, 2.5.2, 3.0, 5.3, 5.6, 5.7, 5.8, 5.9, 5.12, 5.13, 7.1, 7.6, 7.7, 7.9, Appendix IB, Appendix IC, Appendix ID, Appendix III and Appendix IV.

Additionally, under the “Study Regimen” section of the Schema, under Step 3, language has been added to clarify that if a participant on Step 1 or 2 prematurely transitions to annual follow-up or transitions to Step 3 on-study but off study-provided product, non-study provided PrEP may be used (if available) at the discretion of the primary care physician.

See Revisions 4, 5, 13, 14, 15, 21, 23, 24, 25, 26, 28, 29, 36, 38, 39, 40, 48, 49, 50, 51, 54.

4. Per a request from the United States Food and Drug Administration, an additional secondary objective and accompanying statistical analysis is added to compare changes in weight, blood pressure (BP), pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC. These measures are already required to be documented in source documents at each visit (weight, BP, pulse) or entered into the study database (fasting lipid testing at enrollment and Weeks 57 and 105 in Step 2, in which case the glucose already being tested at those same timepoints would also be fasting – the only change to the protocol in this case is that glucose at those timepoints is now also indicated as fasting glucose). As such, weight, BP, pulse, and fasting glucose are now required to be entered into the study database for analysis at the timepoints listed in the revisions below. Fasting lipids will continue to be entered into the study database. Several protocol sections are impacted by the addition of this objective: Schema, 1.15, 2.2, 5.2, 5.3, 5.4, 5.6, 5.9, 7.5.2, 7.11.3, Appendices IA-IC, and Appendix IV.

See Revisions 4, 11, 12, 20, 21, 22, 23, 26, 37, 41, 47, 48, 49, 54.

5. Section 1.2 is updated to remove reference to an outdated version of the cabotegravir Investigator’s Brochure.

See Revision 6.

6. Table 2 and protocol sections 1.3.2, 1.4, 1.4.1, and 1.15 are updated with the latest available clinical data from ongoing and completed CAB trials. Section 1.15 is also a new section that specifically provides the rationale for collecting and analyzing weight, pulse, blood pressure and fasting glucose and lipids.

See Revisions 7, 8, 9, 10, 11.

7. In Section 3.2, text is added as a “Note” to an existing exclusion criterion to clarify that past participation in a monoclonal antibody study is not exclusionary, effective as of Version 1.0 of the protocol.

See Revision 16.

8. In Section 3.6, text requiring CMC consult for early termination visit procedures to be conducted is deleted.

See Revision 17.

9. Section 3.6.1 is a new section added to provide further explanation for procedures for participants who prematurely withdraw consent from the study.

See Revision 18.

10. Several sections in Section 4.0 have been updated or contain new information as follows (and the new information causes several sections to be renumbered:

- Sections 4.2.1 and 4.2.2 are updated for further clarification.
- Section 4.3 (4.3.1 and 4.3.2) is a new section and contains updated instructions for preparation of oral and injectable study product; these instructions have always appeared in the Study Specific Procedures (SSP) Manual; however, per directive from the US FDA, instructions now must appear in the protocol document. The instructions will continue to appear in the SSP Manual as well, and any updates made for the protocol have also been made in the SSP.
- Section 4.4 (4.4.1 and 4.4.2) is updated for clarification.
- Section 4.5 is updated with a minor clarification.
- Section 4.6 adds a new stipulation that if treatment for any condition requiring the use of a prohibited medication is planned, blinded study product will be held and the participant will be offered open label TDF/FTC during the course of prohibited medication use and may return to blinded study product once the prohibited medication use is completed. Sites are instructed to consult the CMC for clinical guidance, as well as Section 9 of the SSP for guidance regarding instructions for the visits in these scenarios. This applies to any participant who stopped blinded study product for this reason prior to all relevant national and local approvals of Version 3.0 of the protocol. Additionally, language is added to further clarify that non-study provided PrEP (TDF/FTC or TAF/FTC for PrEP) is not permitted during any portion of HPTN 083, with the exception that non-study provided PrEP may be used per primary care physician discretion during annual follow-up and during Step 3 when participants are on-study Step 3 but off study-provided PrEP.

Section 4.6 is also updated to include a list of prohibited medications, per directive from the US FDA to include them in the protocol document. This list is also contained in the SSP Manual.

See Revision 19, which depicts all the impacted sections listed above.

11. Section 5.2 is updated per # 4 above. It is also clarified that height is a one-time recording in the source documents and entered into the study database (this is not a new measurement in this amendment. It has been required since Version 1.0 of the protocol to record height in the study source documents at Enrollment as part of the complete physical exam, per the protocol and SSP Manual. The only new requirement in this amendment is to capture this one-time measurement in the study database). Additionally, a new “Note 2” is added to reference the SSP Manual for the schedule of CASI and interviewer-administered assessments.

See Revision 20.

12. Section 5.3 is revised per # 3 and # 4 above. The “Notes” included in the section are also revised to clarify that if an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternative interval for follow-up. Additionally, a note is also added to state that the Week 4 visit must take place within 120 days of enrollment - this is because sites have been advised since the study began to dispense an extra 30-day supply of oral study product at the enrollment visit for a total 60-day supply. Time beyond this 120-day period would not allow for the minimum 50% adherence to oral study product required to proceed from Step 1 to Step 2.

See Revision 21.

13. Section 5.6 is updated per # 3 and # 4 above. It is also updated to state that if a participant who is also participating in the DXA subset prematurely transitions to Step 3, a DXA may be performed per CMC authorization if the participant transitions to Step 3 close to the Week 57 or 105 DXA timepoints.

See Revision 23.

14. Section 5.10 is updated to provide clarification of visit windows and requirements for contacting the CMC for scheduling guidance.

See Revision 27.

15. Section 5.12 is updated per # 3 above. A Note is added referring the reader to Appendix III, where additional guidance is provided for participants who wish to prematurely discontinue injections in Step 2 due to an injection site reaction. For consistency with Appendix ID, procedures for participants who transition to annual visits have been updated to include blood collection.

See Revision 28.

16. Section 5.14.2 is updated to clarify follow-up procedures for participants who become HIV infected during Step 2.

See Revision 30.

17. Section 5.17 is updated to provide guidance for procedures at the next visit following a missed visit.

See Revision 31.

18. Section 5.20 is a new section added to provide guidance for participants who have transitioned early to Step 3 under circumstances that may allow a return to Step 2 to resume blinded study product as determined through consultation with the CMC.

See Revision 32.

19. Per DAIDS RSC, corresponding urls are updated in Sections 6.4, 6.4.1, 6.4.3, and 10.1.
See Revisions 33, 34, 35, 44.
20. Section 7.6 is revised per # 3 under “Summary of Revisions and Rationale” above. It is also revised to correct two typographical errors which were inadvertently included in previous versions of the protocol, and are unrelated to other protocol changes, including changes to study sample size.
See Revision 38.
21. Section 7.11.4 is updated to remove India as a country with sites participating in the study.
See Revision 42.
22. Section 8.6 is updated to include ethics committees as entities that may discontinue the study.
See Revision 43.
23. Section 10.6 is updated to provide additional guidance regarding retention of study records following completion of a study.
See Revision 45.
24. Section 11.0 is updated to add three new references and correct a website address for an existing reference.
See Revision 46.
25. Appendices IA-D are updated per # 3 and # 4 above, including the footnotes in Appendix IC. Footnotes are also updated to include Appendices IE-G for reference to the HIV testing algorithm. Additionally, Appendix IA is updated to add height as a one-time measurement at enrollment, including a corresponding new Footnote # 7.
See Revisions 47, 48, 49, 50.
26. Appendix III is revised as follows: 1) per # 3 above; 2) to state that the CMC may direct an alternative interval for follow-up in the case where an etiology for elevated ALT is identified or persistent without explanation; 3) to state that changes in creatinine clearance of > 30% that are accompanied by a creatinine that remain within normal limits do not need to be reported to the CMC; and 4) to include additional reporting requirements for injection site reactions.
See Revisions 51, 52, 53.
27. Appendix IV Screening and Enrollment Consent Form is updated to reflect changes per items # 3 and 4 above. A new risk is also added regarding a possible injection risk where the injection could enter the skin, blood or a nerve (instead of the muscle), producing a possible vasovagal reaction. This is being added as a result of an incident in a ViiV-sponsored HIV treatment study of injectable CAB and rilpivirine, which resulted in an IND Safety Report distributed to all sites. Procedures for Steps 1, 2, and 3 are updated to clarify metabolic measurements to be obtained during physical exams. The Step 2 Week 153/Step 3 Day 0 visit as well as Annual Visit procedures are updated to include collection of unused oral study product. A note is added to Step 3 to clarify which procedures are required based on the timing of a participant’s entry to Step 3. Additionally, the consent form cover page and signature page are updated to reflect Version 3.0 and the final date of Version 3.0 approval.
See Revision 54.
28. Other minor typographical and grammatical corrections are made throughout the document.

Implementation of Modifications

Modifications of protocol text are described below. Modifications are generally listed in order of appearance in the protocol. Where applicable, modified protocol text is shown using strikethrough for deletions and bold type for additions.

Revision 1: Protocol Title Page

The protocol title page is updated for Version 3.0.

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

DAIDS Document ID: 20725

A Study by the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, National Institute of Allergy and Infectious Diseases

Pharmaceutical Support Provided by:

ViiV Healthcare
Gilead Sciences, Inc

IND # 122, 744

Protocol Chair:

Raphael J. Landovitz, M.D., M.Sc.

Protocol Co-Chair:

Beatriz Grinsztejn, M.D., Ph.D.

Final Version 3.0

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Revision 2: Protocol Signature Page

The protocol signature page is updated for Version 3.0.

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

DAIDS Document ID # 20725

Version ~~2.0~~**3.0**

~~July 25, 2018~~**October 31, 2019**

I will conduct this 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 US 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.

Name of Investigator of Record

Signature of Investigator of Record

Date

Revision 3: Protocol Team Roster

Contact information for Tim Holtz, MD, MPH is updated; Andrea Jennings is added, and David Burns is removed from the roster.

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Revision 4: Schema

For ease of reference, the first three pages of the Schema are depicted below. A new study objective has also been added to the list of secondary objectives; as no other changes are made to the objectives listed in the Schema, only that one new objective is depicted below.

SCHEMA

- Purpose:** To evaluate the safety and efficacy of the injectable agent, cabotegravir (CAB LA), for pre-exposure prophylaxis (PrEP) in HIV-uninfected cisgender men and transgender women who have sex with men (MSM and TGW).
- Design:** Multi-site, double blind, two-arm, randomized (1:1), controlled non-inferiority trial of the efficacy of CAB LA compared to daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC) for HIV prevention.
- Population:** HIV-uninfected MSM and TGW at risk for acquiring HIV infection, ages 18 or older.
- Study Size:** Approximately ~~4500, 2250~~**5000, 2500** per arm.

Study

Duration: ~~Approximately 4~~**Due to staggered timelines of study activation at the participating sites, the overall study duration is approximately 7.5 years.**

Individual participants will be followed on blinded study products for three years from the date of enrollment during Steps 1 and 2. After completion of blinded study products, participants will then receive 48 weeks of open label TDF/FTC during Step 3 – for a total, with of four years of follow-up for any individual participants being followed between 1.5 years (for the latest enrolling participants) to 4.5 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. participant.

In Step 1, participants will receive **blinded daily** oral tablets for 5 weeks. ~~Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual visits until all participants complete Step 2 of the study.~~

In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. ~~Step 2 will be continued until the required number endpoints is reached, estimated to be until Week 153, which is approximately when three years from the final participant reaches 60 weeks on Step 2 (study week 65 for date of the final participant). Participants~~**Enrollment visit. All participants will be all be simultaneously unblinded at after the conclusion of last participant concludes their participation in Step 2.**

In Step 3, ~~all~~ participants will receive **study-provided** open-label daily oral TDF/FTC for up to 48 weeks. ~~Participants in Step 2 who prematurely transition to Step 3 will complete the required 48 weeks of follow up in Step 3, and will then be asked to attend annual visits until all participants in the study complete Step 2. Participants will therefore be~~

~~followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and up to. The timeline for the 48 weeks on open label daily oral TDF/FTC with or without annual follow up). All participants will be transitioned to locally available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study, or if they transition to annual visits in Step 1 or Step 2.~~ **of open label TDF/FTC for Step 3 begins 8 weeks from the last administered injection of Step 2, irrespective of actual date of TDF/FTC initiation.**

Study

Sites:

Study sites ~~will be~~ **are** listed in the Study Specific Procedures (SSP) Manual, and ~~will~~ include sites in the Americas, Asia, and South Africa.

SCHEMA (continued)

Study

Regimen:

Once randomized to one of two arms, participants will move through the following steps (active drugs are shown in bold text):

Step 1:

Arm A – **Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for five weeks

Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for five weeks

A participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product and will be terminated from the study, ~~and referred for HIV-related care. Additionally, participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will remain blinded to their study assignment and be asked to attend annual visits until all participants complete Step 2 of the study.~~ **and referred for HIV-related care.**

Step 2:

Arm A – **CAB LA** (600 mg as a single intramuscular [IM] injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo ~~to~~ **Week 153**

Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at two time points 4 weeks apart and every 8 weeks thereafter (matching vehicle, identical volume as active injectable product in Arm A) ~~to~~ **Week 153**

~~This step will continue until the required number of endpoints is reached.~~

A participant that becomes HIV-infected during Step 2 of the study will permanently discontinue study product, be placed on immediate suppressive ART, and will be followed at quarterly intervals for 52 weeks after their last injection prior to diagnosis of HIV in order to test for safety parameters, as well as CD4 cell count and HIV viral load. After 52 weeks, they will be terminated from the study and transitioned to continued HIV-related care. ~~Additionally, participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will remain blinded to their study assignment and transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual visits until all participants complete Step 2 of the study.~~

Step 3:

Both arms: **Open-label daily oral TDF/FTC** ~~starting no later than 8 weeks after the will start at Week 153 (last injection (in order to cover the pharmacokinetic (PK) tailday of Step 2) /Day 0 (first day of Step 3) and continue for Arm A 48 weeks.~~

~~All participants), and continued for up to 48 weeks. Participants will then transition to~~ **will be transitioned to** locally-available HIV prevention services, including services for PrEP, if available ~~(and, at the end of their participation in the study, or if they~~

transition to annual visits ~~if applicable as outlined above~~; in Step 1 or Step 2, or if at the discretion of the primary care physician, they transition to Step 3 on study but off study-provided TDF/FTC.

A participant with confirmed HIV infection during Step 3 will be placed on ART and followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of the 083HIV@hptn.org group.

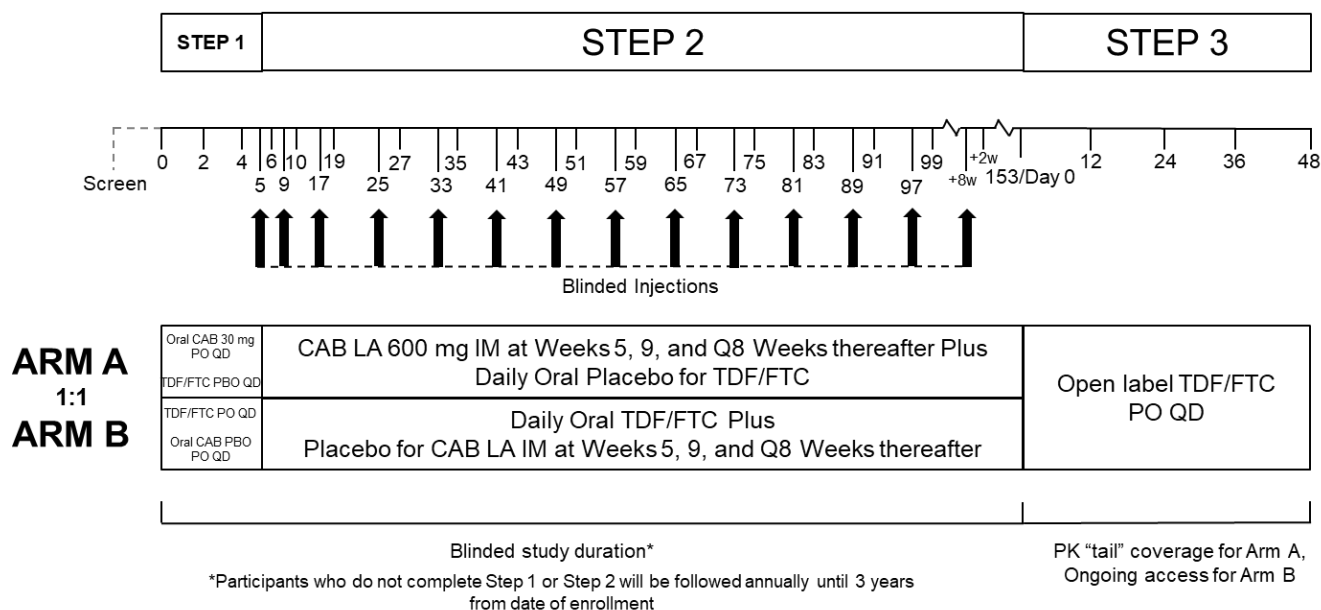
Under Study Objectives in the Schema, the following new secondary objective is added:

- **To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC**

Revision 5: Overview of Study Design and Randomization Scheme

Per # 3 under “Summary of Revisions and Rationale” above, the “Overview of Study Design and Randomization Scheme” has been modified. The first one depicted below is included in Version 2.0 of the protocol, and the second one depicted below is updated and included in Version 3.0 of the protocol. Since this is in picture format, tracked changes are unable to appear.

Version of the picture updated for Version 3.0:



Revision 6: 1.2 Overview of Oral Cabotegravir (Oral CAB) and long-acting injectable (CAB LA)

This section is updated to remove reference to an outdated cabotegravir Investigator’s Brochure.

~~The majority of information contained in this section of the protocol is a summary of information provided in the cabotegravir Investigator’s Brochure V5.0, Effective Date 06 January 2016, unless otherwise noted.~~

Cabotegravir (GSK 1265744) is an investigational HIV integrase strand transfer inhibitor (INSTI) that has attributes favorable for both HIV treatment and prevention indications. Currently in Phase 2 clinical trials, it was initially selected for development based on its potential for a high genetic barrier to resistance and a PK profile that allows low-dose, once-daily oral dosing or monthly to quarterly parenteral dosing using a nanosuspension formulation. An oral tablet version of cabotegravir (oral CAB) is also under development as lead-in therapy to establish acute safety and tolerability in individual subjects prior to switching to the long-acting formulation. CAB LA has a plasma half-life of 21 to 50 days in healthy HIV-uninfected adults.

Revision 7: 1.3.2 CAB LA

This section is updated to include the latest data from HPTN 077.

Additional data through 76 weeks post last injection (an additional 24 weeks longer than the current follow-up of 52-weeks post last injection) in HPTN 077 (which administers CAB LA 800 mg IM every 12 weeks in Cohort 1 and CAB LA 600 mg IM every 8 weeks after two initial injections four weeks apart in Cohort 2) will be available in approximately the fourth quarter of 2017 (for Cohort 1) and the third quarter of 2018 (for Cohort 2). These data will provide additional insight into how long cabotegravir levels may be detected after terminal injection, and help to inform the optimal duration of Step 3 of HPTN 083. **suggests that the median time from the last injection to CAB levels falling below the limits of quantitation (25 ng/mL) were 43.7 (range 20-4-152.5) weeks for males and 67.3 (range 17.7-225.5) weeks for females.**

Revision 8: 1.4 Clinical Experience to Date: Oral CAB and CAB LA

Only one sentence stating the fact that the table is update is depicted below.

Cumulative exposures of ~~GSK-1265744~~ CAB, through ~~December 2017~~ **October 2018**, are shown in Table 2.

Revision 9: Table 2

Due to the large number of formatting changes in the table, the final version of the table in Version 2.0 appears first, followed by the final updated table in Version 3.0 (not shown with tracked changes).

Table 2 included in Version 2.0:

Table 2: Cumulative Cabotegravir Exposure Estimates from Phase 1 through Phase 2b Clinical Studies Up To December 2017

Treatment Population/ Dose	Duration	Completed	Ongoing/ Concluded	Total
Healthy Volunteers/HIV Uninfected				
5 to 150 mg oral	Single dose	223	0	223
10 to 30 mg QD po	10 to 28 days	263	647	910
150 mg q12hr po	3 doses	40	0	40
100 – 800 mg IM/SC LA	Max 456 days	230	504	734
Any dose		584	647	1231
HIV Infected Patients				
5 to 30 mg QD po (Ph 2a)	10 days	15	0	15
10 to 60 mg QD po (Ph 2b)	Max 1946 days	0	181	181
30 mg QD po (Ph 2b/3/other)	Max 1313 days	0	944	944
Up to 800 mg IM LA	Max 1176 days	0	880	880
Any dose		15	1130	1145
ALL Participants				

Single dose oral (5 to 150 mg)		223	0	223
Repeat dose QD po (5-60 mg)		278	1772	2050
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA injection (100 to 800 mg)		230	1384	1614
Any dose		599	1777	2376

Updated Table 2 in Version 3.0:

Table 2. Cumulative CAB Exposures from Phase 1 through Phase 3 Clinical Studies Through October 2018

Treatment Population/ Dose	Duration	Completed	Ongoing/ Concluded^a	Total
<i>Healthy Volunteers/HIV-Uninfected</i>				
5 to 150 mg oral	Single dose	208	0	208
10 to 30 mg once daily oral	10 to 28 days	293	1694	1987
150 mg every 12 hours oral	3 doses	40	0	40
100 – 800 mg IM/SC LA	Max 763 days ^g	230 ^b	1377 ^c	1607
Any dose		599	1694	2293
<i>HIV-infected patients</i>				
5 to 30 mg once daily oral (Ph 2a)	10 days	15	0	15
10 to 60 mg once daily oral (Ph 2b)	Max 2247 days ^h	0	181	181
30 mg once daily oral (Ph 2b)		0	1739	1739
Up to 800 mg IM LA ^d	Max 1477 days ^g	0	1745 ^e	1745
Any dose		15	1928	1943
<i>All participants</i>				
Single dose oral (5 to 150 mg)		208	0	208
Repeat dose once daily oral (5 to 60 mg)		308	3614	3922
150 mg oral every 12 hours x 3		40	0	40
Single or repeat dose LA injection (100 to 800 mg)		230 ^b	3122 ^f	3352
Any dose		614	3622	4236

a. Concluded studies: study completed through follow-up; and/or clinical study report is in preparation

b. 172 participants received both oral and LA dosing

c. All participants received both oral and LA dosing

d. Includes 400 mg Q4W and 600 mg Q8W dosing

e. 1736 participants received both oral and LA dosing

f. 3113 participants received both oral and LA dosing

g. Detectable CAB concentrations can remain for up to 72 weeks following the last CAB injection
h. As of 28 Dec 2014, all participants had transitioned to CAB 30 mg in the Open-Label phase of study LAI116482 (LATTE-1), therefore, the longer durations apply to the 30 mg dose only

Revision 10: 1.4.1 Evidence for Clinically Significant Anti-viral Activity in HIV-infected Individuals

As described above, two Phase 2b clinical trials are ongoing (GSK protocol LAI116482 [LATTE] and 200056 [LATTE-2]). In the LATTE study, 181 participants were randomized to receive oral CAB (10, 30, or 60 mg once-daily, blinded doses) in combination with either TDF/FTC or abacavir-lamivudine (ABC/3TC).⁴⁸ An additional 62 participants were randomized to a control arm of open-label efavirenz (EFV) 600 mg once daily in combination with one of the two NRTIs. A week 24 interim analysis demonstrated good initial efficacy and safety of oral CAB in combination with NRTIs. The overall response rate across the three dosing arms of oral CAB were 87% <50 c/mL (FDA snapshot analysis) with minimal differences between oral CAB doses; the control arm response rate was 74% <50 c/mL. In the “maintenance” phase, participants randomized to any of the oral CAB doses who had viral loads <50 c/mL prior to week 24 were transitioned to a regimen maintaining their oral CAB dosing but substituting oral rilpivirine (RPV) 25 mg daily for the NRTI. EFV-treated participants were kept on their “induction” regimen of dual NRTIs with EFV. 96-week data (representing 72 weeks of maintenance dosing) showed virologic suppression (<50 c/mL) rates via snapshot analysis to be 79%, 85% and 93% for oral CAB administered at 10 mg, 30 mg, and 60 mg daily, and 83% for the EFV control participants. One participant randomized to oral CAB 10 mg who successfully transitioned to RPV plus oral CAB 10 mg daily experienced virologic failure at week 48 in the context of sub therapeutic (<50% expected) CAB and RPV plasma levels (partially confounded by an extreme calorie-restricted diet during weeks 40-48), and developed treatment-emergent high level integrase (Q148R) and non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance with the E138Q mutation.⁴⁸ Two additional participants experienced virologic failure on CAB-containing therapy with evidence of NNRTI-resistance only (K101K/E and E183E/K at weeks 48 and 72, respectively).⁵⁰ Two phase 3 trials of CAB LA + RPV LA administered at 4-week intervals for maintenance of virologic suppression in HIV-infected individuals ~~are fully enrolled and ongoing~~ **have been presented (ATLAS, FLAIR), wherein CAB LA + RPV LA was found to be non-inferior to oral ART in both naïve treatment settings (after ABC/3TC/DTG induction to suppression) and as non-failure switch from stably suppressive ART;** an additional phase 3b trial of CAB LA + RPV LA administered at 8-week intervals for maintenance of virologic suppression in HIV infected individuals is ~~also~~ ongoing (ATLAS-2M).

Revision 11: 1.15 Rationale For Collecting and Analyzing Metabolic Parameters

Per # 4 under “Summary of Revisions and Rationale” above, an additional section is added:

Data increasingly support the association of integrase inhibitors with weight gain in the setting of HIV infection. The precise mechanism is unknown, is noted to be greater in Black participants, in women, and in those with lower CD4 cell counts, and appear to be additionally contributed to by the choice of nucleoside analogue reverse transcriptase inhibitors (NRTIs) used as part of the treatment regimen.^{87,88} The contribution of the HIV-associated inflammatory milieu is also unknown. HPTN 077 did not find a difference between CAB and placebo arms for weight gain for any population.⁸⁹ The HPTN 083 study will capture participant data for weight in a standardized

way to evaluate changes between study product arms. Per FDA guidance, additional metabolic parameters (including but not limited to weight, pulse, blood pressure and fasting glucose/lipids) will also be analyzed for changes between study arms.⁹⁰

Revision 12: 2.2 Secondary Objectives

Per # 4 under “Summary of Revisions and Rationale” above, an additional secondary objective is added. Only the new objective is depicted below:

- **To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC**

Revision 13: 2.5 Study Design and Overview

Per # 3 under “Summary of Revisions and Rationale” above, several revisions are made to this section:

This is a Phase 2b/3, randomized, multi-site, two-arm, study of CAB LA compared to daily oral TDF/FTC for HIV prevention. **Approximately 4500 5000** participants will be enrolled, randomized 1:1 to Arm A and Arm B through the following 3 steps:

Step 1:

- Arm A - Daily oral CAB (30 mg tablets) and daily oral placebo for TDF/FTC for 5 weeks.
- Arm B - Daily oral TDF/FTC and daily oral placebo for CAB for 5 weeks.

Any participant that becomes HIV-infected during Step 1 of the study will permanently discontinue study product and will be terminated from the study, and referred for HIV-related care. Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will remain blinded to their study assignment and be asked to attend annual visits until ~~all participants~~ **they each individually complete ~~Step 2~~ 3 years of follow-up from the study-time of Enrollment.**

Step 2:

- Arm A – Injections of CAB LA at two time points four weeks apart and every 8 weeks thereafter beginning at Week 5, and daily oral placebo for TDF/FTC. Injections will consist of 600 mg of CAB LA administered as one 3 mL injection.
- Arm B: Daily oral TDF/FTC and injections of placebo for CAB LA on the same schedule as Arm A beginning at week 5. Injections will consist of the same volume (3 mL) as Arm A participants.

This step will continue until ~~the required number of incident HIV endpoints is reached, estimated to be when the final three years of follow-up, to Week 153, for each participant reaches approximately 60 weeks on Step 2 (study week 65 for the final participant).~~ , **with the last injection provided and the last blinded oral study product dispensed at Week 145.** Participants in ~~Step 2~~ who prematurely stop receiving injections **discontinue blinded study products during Step 2 (having received at least one**

injection) for any reason other than HIV infection will ~~remain blinded to their study assignment and, transition to Step 3, complete the required~~ **and receive 48 weeks of follow-up in Step 3, and will then be study-provided open label TDF/FTC, followed by annual follow-up until three years from the date of Enrollment. For these participants, the timepoint at which they** transition to Step 3, ~~complete the required 48 weeks of follow-up in Step 3, and~~ **will determine whether they will then be** asked to attend annual visits ~~until all participants complete Step 2 of the study.~~ **following the completion of Step 3; if the completion of Step 3 post-dates three years from the date of Enrollment, annual follow-up is not required.**

All participants will also be simultaneously unblinded after the last participant concludes their participation in Step 2.

Any participant that becomes HIV infected during Step 2 of the study will permanently discontinue study product and will be followed at quarterly intervals for approximately ~~52~~**48** weeks in order to test for safety parameters, as well as CD4 cell count and HIV viral load.

Step 3:

~~When Participants who complete the study reaches the required number full three years of incident HIV endpoints or when the last participant enrolled completes their participation follow-up in Step 2, all~~ **at the Week 153 visit will ideally begin Step 3 on the same day, which will be considered Day 0 of Step 3. On this day,** participants will be unblinded. ~~All participants will begin study-provided~~ open-label daily oral TDF/FTC for approximately ~~48~~ weeks (for Arm A, to “cover the tail” ~~starting on~~). **For participants who prematurely transition to Step 3 before completing three years of follow-up in Step 2, Step 3 will start no** later than 8 weeks after their last injection (the timing of the last injection visit and duration of provision of daily oral TDF/FTC may vary according to when the last participant reaches their final Step 2 visit or if the study endpoints are reached earlier).

All participants will be transitioned to locally-available HIV prevention services, **including services for PrEP, if available,** when their participation in the study ends, or if they transition to annual visits in Step 1 or Step 2, or if at the discretion of the primary care physician, they transition to Step 3 ~~ends. on study but off study-provided TDF/FTC.~~

Revision 14: 2.5.2 Study Duration

This section is revised per # 3 under “Summary of Revisions and Rationale”; as the details in this section already appear (and are updated) in the Schema and Section 2.5, text is reduced for greater simplicity and clarification.

~~The study will last approximately 4.5 years total, with individual participants being followed between 1.5 years (for the latest enrolling participants) to 4.5 years (for the earliest enrolling participants). Accrual will require approximately 130 weeks. In Step 1, participants will receive oral tablets for 5 weeks. In Step 2, participants will receive injections (as a single injection at two time points 4 weeks apart and every 8 weeks thereafter) and daily oral tablets. Step 2 will be continued until the required number endpoints is reached, estimated to be approximately when the final participant reaches their last scheduled visit in Step 2 (approximately week 65 for the final participant). Participants will be all simultaneously unblinded at the conclusion of Step 2. In Step 3, all participants will receive open label~~

~~daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed between 113 weeks to 233 weeks (between 65 and 185 weeks on blinded study medication and for Arm A participants up to 48 weeks on open-label daily oral TDF/FTC). All participants will be transitioned to locally available HIV prevention services, including services for PrEP, if available, at the end of their participation in the study.~~

The study will last approximately 7.5 years total, with individual participants being followed for approximately 4.0 years total. Accrual will require approximately 3.5 years.

Revision 15: 3.0 Study Population

Section 3.0 is revised per # 3 under “Summary of Revisions and Rationale” above:

~~Four~~ **Approximately five** thousand five hundred ~~(4500)~~ **(5000)** HIV-uninfected MSM and TGW will be included in this study. Each site will be asked to work with their Community Advisory Board and outreach, education and recruitment teams to develop a recruitment plan appropriate for their local population.

Revision 16: 3.2 Exclusion Criteria

- Past or current participation in HIV vaccine trial. An exception will be made for participants that can provide documentation of receipt of placebo (not active arm). **Note: Past participation in a monoclonal antibody study is not exclusionary, effective as of Version 1.0 of HPTN 083.**

Revision 17: 3.6 Participant Withdrawal

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the final protocol-dictated study week, and study staff will record the reason(s) for all withdrawals from the study in participants’ study records. ~~In such cases, the Investigator of Record or designee must contact the CMC for guidance regarding final evaluation procedures.~~

Revision 18: 3.6.1 Premature Termination Visits

In general, for participants who withdraw consent from the study prematurely during a study visit, the requirements for that visit should be completed to the extent possible except for provision of study product and will be considered their final visit. When possible, a plan should be made to provide final laboratory results to the participant. For participants who inform the site in between visits that they wish to withdraw consent from the study, sites should make every effort to have the participant return any unused study product.

Revision 19: 4.0 Study Product Considerations

All updates made to section 4.0 are depicted.

4.2.1 Oral product Products

~~Oral CAB 30 mg tablets~~ **30 mg (blinded)** are formulated as white to almost white oval-shaped coated tablets for oral administration. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain **30 tablets and a desiccant. The tablets must be stored in the original container.** The bottles ~~should~~ **are to be stored up to 30 degrees Celsius (30°C, 86° Fahrenheit (86°F))** and protected from moisture.

~~Placebo for CAB 30 mg tablets for oral CAB (blinded)~~ are formulated as white to almost white oval-shaped coated tablets to visually match the ~~active oral CAB~~ tablets. The tablets are packaged in high density polyethylene (HDPE) bottles with child-resistant closure that include an induction seal. The bottles contain **30 tablets and a desiccant. The tablets must be stored in the original container.** The bottles ~~should~~ **are to be stored up to 30 degrees Celsius (30°C, 86° Fahrenheit (86°F))** and protected from moisture.

~~TDF 300 mg/FTC 200 mg/TDF 300 mg study product tablets (blinded)~~ are ~~manufactured and provided by Gilead Sciences, Inc. under the trade name Truvada®.~~ **TDF/FTC capsule-shaped, film-coated blue tablets that must be stored in the pharmacy in the original container.** Each bottle contains a silica gel desiccant canister to protect the product from humidity. ~~Store at~~ **The bottles are to be stored up to 25°C (77°F).** Excursions are permitted between 15° to 30°C. ~~Matching placebo tablets also will be provided by Gilead Sciences, Inc. (59 to 86°F).~~

~~Placebo for TDF 300 mg/FTC 200 mg tablets (blinded)~~ are ~~capsule-shaped, film-coated blue tablets that visually match the TDF/FTC tablets in physical size and appearance.~~ The tablets are packaged in bottles with a child-resistant cap. ~~In addition to~~ **must be stored in the tablets, the original container.** ~~Each~~ bottle contains a silica gel desiccant to protect ~~the product~~ **the product** from humidity. The bottles ~~should~~ **are to be stored at up to 25°C (77°F).** Excursions are permitted between 15°C to 30°C. ~~(59 to 86°F).~~

TDF 300 mg/FTC 200 mg tablets (open-label) are capsule-shaped, film-coated blue tablets that must be stored in the original container. Each bottle contains a silica gel desiccant canister to protect the product from humidity. The bottles are to be stored at 25°C (77°F). Excursions are permitted between 15° to 30°C (59 to 86°F). The TDF/FTC fixed dose combination tablet containing 300 mg of TDF and 200 mg of FTC is available as Truvada® and is approved by the U.S. FDA for treatment and prevention of HIV-1 infection. Further information on Truvada® is available in the current package insert.⁹¹

Section 4.2.2 Injectable Suspension

~~CAB LA is formulated as a sterile white to slightly colored suspension containing 200 mg/mL of CAB LA for administration by intramuscular (IM). The product is packaged in a glass vial. Each vial is for single use containing a nominal fill of 2mL (400 mg) or 3mL (600 mg), and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30 degrees Celsius (30°C), do not freeze. The CAB study product (oral and LA injectable) Placebo for CAB LA Injectable Suspension will be Intralipid 20% fat emulsion infusion. The cabotegravir study product being tested in this study is investigational and not yet approved by the US FDA for the treatment or prevention of~~

HIV-1 infection. Further information on the study product is available in the Investigator's Brochure (IB), which will be provided by the DAIDS Regulatory Support Center (RSC).

CAB LA is formulated as a sterile white to slightly pink colored suspension containing 200 mg/mL of CAB LA for administration by IM. The product is packaged in a 2 mL or 3 mL glass vial. Each vial is for single use containing 2 mL (400 mg) or 3 mL (600 mg) and does not require dilution prior to administration. CAB LA injectable suspension is to be stored up to 30°C (86°F), do not freeze.

Placebo for CAB LA Injectable Suspension will be Intralipid 20% fat emulsion infusion. The TDF/FTC fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF is available as Truvada® and is approved by the U.S. FDA for treatment and prevention of HIV-1 infection. Further information on Truvada® is available in the current package insert.^{9†} which is packaged in 100 mL IV bags. Intralipid 20% fat emulsion infusion IV bags are to be stored below 25°C (77°F), do not freeze.

4.3 Study Product Preparation

4.3.1 Preparation of the Oral Study Product

The oral products for this study will be provided with customary two-part structure which includes a tear-off portion containing the un-blinded-product identification (i.e., active or placebo).

Prior to dispensing, the un-blinded portion of the tear-off label must be removed and attached to the participant specific pharmacy record such as participant prescription or participant specific study product accountability record. The permanently affixed section of the label will remain on the original container.

The site pharmacist will label the bottle with a participant specific label prior to dispensing. The participant specific label must be in accordance with the local regulations and the DAIDS Pharmacy Guidelines manual.

The pharmacist will prepare the participant-specific study product and dispense sufficient quantity to last until the next follow-up visit plus approximately one-month buffer supply. Pharmacists will record dispensations on the Pharmacy Accountability Logs.

4.3.2 Preparation of Injectable Study Product

The site pharmacist(s) must be proficient in the preparation of injectable study products using aseptic technique under a pharmacy biological safety cabinet (BSC) Class II or better. Local regulations and site institutional policies and procedures for use of personal protective equipment, such as gloves, gowns, masks, and safety glasses, must be followed.

Preparation of Active Injectable Study Product (CAB LA 600 mg/3 mL)

The designated pharmacy personnel will follow the steps below for preparation of active injectable study product, CAB LA injectable suspension. In Step 2 of the study, for the participants in Arm A, one syringe containing 3 mL (600 mg) of CAB-LA must be prepared using aseptic technique under a pharmacy BSC/Isolator.

Materials required for preparation and administration of CAB LA 600mg; 3 mL dose:

1. One CAB LA 600 mg/3 mL vial or two CAB LA 400 mg/2 mL vials
2. Becton Dickenson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent
3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent
4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)
5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent). Refer to the HPTN 083 SSP for further details on appropriate needle gauge size and length to use for IM administration.

Preparation Steps:

1. Remove two vials of CAB LA (400 mg/2 mL per vial) or one vial of CAB LA (600 mg/3 mL per vial) from storage. If the vials are stored in the refrigerator (2°C to 8°C), remove vial(s) from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.
2. Vigorously shake the vial(s) for a full 10 seconds by shaking the vial(s) with long arm movements.
3. Invert the vial(s) and inspect to ensure uniform suspension. If solid remains undispersed, repeat Steps 2-3 until all material is uniformly suspended.

NOTE: It is normal to see small air bubbles at the end of shaking the vial for re-suspension.

4. Using aseptic technique under a pharmacy BSC/isolator, flip off the plastic cap from the vial. Wipe the top of the vial with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry. Do not touch the rubber stopper at any time.
5. Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.
6. With the needle sheath on, pull the syringe plunger rod to allow approximately 1 mL of air into the syringe. Remove the needle sheath.
7. With the vial in the inverted position and the syringe with the needle in the upright position, push the needle through the vial stopper and inject approximately 1 mL of air into the vial.

8. While keeping the syringe with the needle in the upright position, withdraw needed volume of CAB LA suspension from the vial(s) into the syringe
 - Withdraw total of 3 mL (600 mg) of CAB LA suspension from the vial(s) into a syringe.
 - If using two CAB LA 400 mg/2 mL vials to prepare the dose, a second new aspiration needle should be used to withdraw suspension from the second vial. Remove the first needle that was used to withdraw the suspension out of the first vial and discard properly. Attach the new 21G x 1½ inch needle (or equivalent) to the syringe already containing suspension per instructions in Step 5 and repeat Steps 6 and 7 to withdraw the remaining needed volume from the second vial.

Since the suspension can contain some air after having shaken the vial, withdraw enough suspension from the vial in order to be able to de-aerate the syringe properly.

9. Remove the needle that was used to withdraw the suspension out of the vial and discard the needle properly.
10. Place an overlay around the prepared syringe to maintain the blind.
11. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared CAB LA syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

NOTE: The participant-specific prepared CAB LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL). If needed, collect the excess suspension in a beaker to avoid spilling.

12. Record the time that the suspension was withdrawn from the vial and into the syringe in the participant's pharmacy log. This is the time of preparation.
13. Label the prepared syringe containing 3 mL (600 mg) of CAB-LA in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.

After withdrawal of the CAB-LA suspension from the vial into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing the contents of the vial(s) into a syringe (Step 8) and administration to the study participant.

The prepared CAB LA study product in a syringe must be stored at controlled room temperature between 20°C to 25°C (68°F-77°F) from the time it is withdrawn into a syringe to the time it is administered.

Any entered vials or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

Preparation of Placebo Injectable Study Product (Intralipid 20%/ 3 mL syringe)

The designated pharmacy personnel will follow the steps below for preparation of placebo injectable study product. Placebo for CAB LA injectable suspension is Intralipid 20% fat emulsion infusion. In Step 2 of the study, for the participants in Arm B, one syringe containing 3mL of intralipid 20% fat emulsion infusion will be prepared using aseptic technique under a pharmacy BSC/Isolator.

Materials required for preparation and administration Placebo for CAB LA (Intralipid 20%) 3 mL dose:

- 1. One 100 mL IV bag of intralipid 20% fat emulsion**
- 2. Becton Dickenson (BD) 3-mL syringe, Leur-Lok Tip, Product No.: 309657 or equivalent**
- 3. Becton Dickinson (BD) 5-mL Syringe, Luer-Lok Tip, Product No.: 309646 or equivalent**
- 4. Needle for aspiration: BD general use sterile hypodermic needle, 21G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305165 or equivalent)**
- 5. Needle for intramuscular injection: BD IM sterile hypodermic needle, 23G x 1½ inch (e.g. PrecisionGlide Needle, Product No.: 305194 or equivalent)**

Preparation Steps:

- 1. Remove one 100 mL IV bag of Intralipid 20% from storage. If the bags are stored in the refrigerator (2°C to 8°C), remove bag from the refrigerator and wait at least 15 minutes to equilibrate to room temperature.**
- 2. Using aseptic technique under a pharmacy BSC/ Isolator, wipe the additive port of the infusion bag with an alcohol pad (isopropyl alcohol 70% or similar) and allow to dry.**
- 3. Remove a 3 mL or 5 mL size syringe and 21G x 1½ inch (or equivalent) needle for aspiration. Attach the needle to the Luer connection of the syringe.**
- 4. Remove the needle sheath.**
- 5. Push the needle through the additive port of the infusion bag and withdraw 3mL of Intralipid 20% into the syringe.**
- 6. Since the suspension can still contain some air, withdraw enough suspension from the Intralipid 20% IV bag in order to be able to de-aerate the syringe properly.**
- 7. Remove the needle that was used to withdraw the suspension out of the Intralipid IV bag and discard the needle properly.**

8. Place an overlay around the dosing syringe to maintain the blind.
9. Attach a 23G x 1½ inch (or equivalent) needle to the Luer connection of the prepared Intralipid 20% (placebo) syringe for IM injection for the participant. Alternatively, the site pharmacist can attach a syringe cap to the prepared syringe. The study staff can then attach the appropriate needle for administration to the prepared syringe in the clinic before administration.

NOTE: The participant-specific prepared Intralipid 20% syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

De-aerate the syringe by first tapping with a finger against the syringe and then by moving the plunger rod carefully forward with the needle in an upright position until the first drop of suspension appears. Remove the excess suspension in order to administer the correct volume (3 mL). If needed, collect the excess suspension in a beaker to avoid spilling.

10. Record the time the suspension was withdrawn from the Intralipid 20% IV bag into the syringe in the participant's pharmacy log. This is the time of preparation.
11. Label the prepared syringe containing 3 mL of Intralipid 20% suspension in a blinded fashion as "CAB LA 600 mg or Placebo for CAB LA", including the volume (3 mL), route (IM), participant's PTID, date and time of preparation, and date and time of expiration. Follow the DAIDS Pharmacy guidelines and local regulations for preparing the participant specific label.
12. Any entered IV bag or expired filled syringes should be disposed of in accordance with institutional or pharmacy policy.

After withdrawal of the Intralipid 20% suspension from the IV bag into a syringe, it is recommended to inject the suspension immediately. Do not exceed 2 hours between withdrawing from the IV bag into a syringe (Step 5) and administration to the study participant. The prepared Placebo for CAB LA study product in a syringe must be stored at controlled room temperature between 20° C to 25° C (68° F-77° F) from the time it is withdrawn into a syringe to the time it is administered.

4.4 Study Product Acquisition and Accountability

Cabotegravir study product (oral (CAB) 30 mg tablets, Placebo for CAB tablets, and Cabotegravir Long Acting (CAB LA) is being injectables are manufactured and provided by ViiV Healthcare. Intralipid 20% IV bags are manufactured by Fresenius Kabi and provided by ViiV Healthcare. TDF 300 mg/FTC oral study product is being 200 mg tablets and Placebo for TDF/FTC tablets are manufactured and provided by Gilead Sciences, Inc.

4.4.2 Study Product Accountability

The site pharmacist is required to maintain complete records of all study products received from the CRPMC and subsequently dispensed to study participants. All study products must be stored in the pharmacy. ~~At~~ **At US clinical research sites, all unused study products must be returned to the CRPMC**

after the study is completed, terminated or otherwise instructed by the study sponsor. The procedures to be followed are provided in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks. **The site pharmacist at non-US clinical research sites must follow the instructions in the Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks DAIDS Pharmaceutical Affairs for the destruction of unused study products.**

4.6 Concomitant, Prohibited, and Precautionary Medications

~~Information regarding prohibited and precautionary concomitant medications can be found in the SSP Manual. The SSP Manual will be revised (as a whole or as a Memorandum of Changes) and re-issued when changes are made.~~ **As noted in the SSP Manual Section 9, a variety of medications including rifampicin, rifapentine and rifabutin are contraindicated for concurrent use with cabotegravir. If treatment for any condition requiring the use of a prohibited medication (including but not limited to TB or LTBI) is planned, blinded study product should be held. Depending on which step the participant is in, the participant will be offered study-provided open label TDF/FTC during the course of prohibited medication use and may return to blinded study product once the prohibited medication use is completed. This is also applicable to any participant who stopped blinded study product prior to all relevant national and local approvals of Version 3.0 of the protocol. Sites must contact the CMC for clinical guidance on implementation of this blinded study product hold, concurrence on the appropriateness of planned resumption of blinded study products upon prohibited medication completion, and resumption of blinded study products when/if appropriate. Section 9 of the SSP provides guidance regarding the visit schedule during the use of study-provided open label TDF/FTC while using a prohibited medication.**

As also outlined in the SSP Manual Section 9, non-study provided TDF/FTC or TAF/FTC for PrEP is not permitted during any portion of HPTN 083. Exceptions to this include that non-study provided PrEP may be used per primary care physician discretion during annual follow-up (when participants are off study-provided product per protocol) and during Step 3 *in circumstances in which a participant is not on study-provided open label TDF/FTC per protocol* (e.g., in the case of an AE).

The precautionary and prohibited medications are:

Cabotegravir:

- **Not to be administered concurrently:**
 - **Cytotoxic chemotherapy or radiation therapy**
 - **Systemically administered immunomodulators**
 - **NOTE: Stable physiologic glucocorticoid doses (defined as prednisone ≤ 15 mg/day or equivalent as a stable or tapering dose) are not prohibited. Use of corticosteroids for an acute condition such as asthma exacerbation, or receiving a short course (defined as ≤ 2 weeks of pharmacologic glucocorticoid therapy) is also not prohibited**
 - **barbiturates**
 - **carbamazepine**
 - **oxcarbazepine**
 - **phenytoin**
 - **pheonobarbital**

- rifabutin
- rifampin
- rifapentine
- St. John's wort
- **Prohibited within 7 days before and 7 days after an injection**
 - high dose aspirin (>325 mg per day)
 - anagrelide
 - apixaban
 - argatroban
 - bivalirudin
 - clopidogrel
 - dabigatran
 - dalteparin
 - enoxaparin
 - fondaparinux
 - heparin
 - lepirudin
 - prasugrel
 - rivaroxaban
 - ticagrelor
 - ticlopidine
 - warfarin
- **Oral formulation precautions**
 - Antacid products containing divalent cations (e.g., aluminum, calcium, and magnesium) must be taken at least 2 hours before or at least 4-6 hours after the oral CAB administration

Truvada:

- **Medications containing the following ingredients should not be administered concurrently:**
 - emtricitabine or tenofovir disoproxil fumarate (e.g. ATRIPLA®, COMPLERA®, EMTRIVA, GENVOYA®, ODEFSEY®, STRIBILD®, or VIREAD, Descory).
 - lamivudine (e.g. Combivir, Dutrebis, Epivir, Epivir-HBV, Epivir A/F, Epzicom, Triumeq, or Trizivir)
 - adefovir (e.g. HEPSERA®)
 - tenofovir alafenamide (e.g. Vemlidy)
 - didanosine (e.g. Videx EC)
 - atazanavir (e.g. Reyataz, Evotaz (atazanari/cobicistat))
 - ledipasvir/sofosbuvir (e.g. HARVONI®)
 - darunavir (e.g. Prezista)
 - lopinavir/ritonavir (e.g. Kaletra)

- orlistat (e.g. Alli, Xenical)

Intralipid 20% fat emulsion: There are no precautionary/prohibited medications in the current package insert for Intralipid 20% fat emulsion.

Additional information regarding recommended, prohibited, and precautionary concomitant medications can be found in the cabotegravir IB and the Truvada® PI.

The precautionary and prohibited medications listed above are also included in Section 9 of the SSP Manual; refer to that section for other information.

Revision 20: 5.2 Step 1: Week 0 – Enrollment

Only the sections impacted are depicted below:

Clinical Procedures

- Complete medical history and complete physical exam, **per section 9 of the SSP Manual, including concomitant medications, as well as height, weight, blood pressure, and pulse data entry into Medidata Rave (the complete medical history and complete physical exam may be performed during screening at the discretion of the Investigator of Record or their designee).**
Note: The collection of height is a one-time data entry into Medidata Rave.

Laboratory Evaluations

- HIV testing (see SSP Manual)
- Hepatitis B testing (HBsAb and HBcAb required at enrollment)
- CBC with differential
- Chemistry testing (see Appendix IA)
- Liver function testing (see Appendix IA)
- Fasting lipid profile **and fasting glucose** (participants should be fasting for at least 8 [preferably 12] hours prior to sample collection) (see Appendix IA)

Note 2: Throughout this section, the CASI and interviewer-administered assessments are referred to as “behavioral” and “acceptability” assessments. Refer to the SSP Manual Schedule of Forms for the schedule of CASI and interviewer-administered assessments.

Revision 21: 5.3 Step 1: Weeks 2 and 4 – Oral Safety Visits

Only the sections impacted are depicted below:

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications, **as well as weight, blood pressure, and pulse data entry to Medidata Rave**

NOTES for Weeks 2 and 4:

All HIV test results from previous visits and at least one HIV test result from the current visit must be available and reviewed. If any of these tests is reactive/positive, study drug should be discontinued.

A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is < Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is < Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If ~~the repeated~~ value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment**. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to < Grade 1. **If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.**

A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment**. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to < Grade 1. **If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.**

Excluding ALT, any grade 3 clinical or laboratory AE observed prior to Week 5 will prompt consultation with the CMC prior to any injectable dosing.

Grade 3 adverse events deemed related to study product, or a Grade 3 ALT, or any Grade 4 adverse event will lead to permanent study product discontinuation, and the participant will be followed annually until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment**. AEs will be followed until resolution (< grade 1) in consultation with the CMC.

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment**. All such cases must be reported to the CMC.

The Week 4 visit must take place within 120 days of study enrollment. Participants with pill counts resulting in less than 50% adherence as assessed by pill count at the Week 4 visit will not be allowed to transition to Step 2. These participants will be asked to report for annual visits until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment**. Refer to Section 5 of the SSP for instructions regarding participants who forget to bring their pill bottles to the Week 4 visit.

Revision 22: 5.4 Step 2: Weeks 5 – First injection visit in Step 2

This section is revised per # 4 under “Summary of Revisions and Rationale” above:

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications, **as well as weight, blood pressure, and pulse data entry to Medidata Rave**

Revision 23: 5.6 Step 2: All remaining visits where injections occur

This section is revised per # 3 and # 4 under “Summary of Revisions and Rationale” above:

Step 2: All remaining visits where injections occur - Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, ~~153, 161, 169, 177, 185~~

Administrative, Behavioral, and Regulatory Procedures

- Locator information
- HIV counseling
- Offer condoms and lubricant
- Behavioral assessment (only at Weeks 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, 137, ~~153, 169, 185~~)
- Acceptability assessment (only at Weeks 17, 41, 65, 89, 137, ~~and 185~~)

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications, **as well as weight, blood pressure, and pulse data entry to Medidata Rave**
- ECG (only at Weeks 57, 105, ~~153~~)
- BMD Subset only (only at Weeks 57 and 105): DXA scan, and dietary calcium and Vitamin D assessment. These scans may be performed +/- 8 weeks of each visit).

Note: If a participant in the BMD subset prematurely transitions out of Step 2 to Step 3 or annual visits, and the transition occurs close to the Week 57 or Week 105 DXA timepoints, the CMC may authorize that a DXA be performed

- Blood collection
- Urine collection for urinalysis (only at Weeks 57, 105, ~~153~~)
- Urine collection for GC/CT testing (only at Weeks 33, 57, 81, 105, 129, ~~153, 177~~)
- Rectal swab for GC/CT testing (only at Weeks 33, 57, 81, 105, 129, ~~153, 177~~)
- Administer injection
- Dispense pills

Laboratory Evaluations

- HIV testing (see SSP Manual)
- HCV testing (only at Weeks 57, 105, ~~153~~)
- CBC with differential

- Chemistry testing (see Appendix IB)
- Liver function testing (see Appendix IB)
- Fasting lipid profile **and fasting glucose** (only at Weeks 57, 105) (see Appendix IB)
- Syphilis serologic testing (only at Weeks 33, 57, 81, 105, 129, ~~153, 177~~)
- Urinalysis (only at Weeks 57, 105, ~~153~~)
- Urine GC/CT testing (only at Weeks 33, 57, 81, 105, 129, ~~153, 177~~)
- Rectal swab GC/CT testing (only at Weeks 33, 57, 81, 105, 129, ~~153, 177~~)
- Plasma storage
- DBS storage

Revision 24: 5.7 Step 2: All remaining safety visits

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

Step 2: All remaining safety visits, with Week 10 occurring 1 week after the Week 9 injection, and every 2 weeks after each injection visit thereafter as - Weeks 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, ~~155, 163, 171, 179, 187~~

Revision 25: 5.8 Week 153, Last Visit of Step 2/Day 0, First Visit of Step 3

This section is new per # 3 under “Summary of Revisions and Rationale” above:

The final visit of Step 2 will take place at Week 153, which is also Day 0 of Step 3. An injection will not be administered at this visit and blinded oral study product will not be dispensed at this visit. All other procedures required for Week 153/Day 0 will be performed. Any remaining blinded oral study product will be collected from the participant as part of the conclusion of Step 2. Open-label oral product will be dispensed at this visit as part of Day 0 of Step 3. The procedures required at Week 153 (except for administration of the injection) and results of testing from Week 153 will also apply to Day 0 of Step 3 unless otherwise noted below and otherwise directed by the CMC. Additionally, if the Week 153 visit is missed or has already occurred or passed at the time Version 3.0 of the protocol is approved and implemented at a site, the final visit of Step 2/first visit of Step 3 will take place at the next visit the participant attends; the CMC may be contacted if additional guidance is required in these cases, though this is not required.

Administrative, Behavioral, and Regulatory Procedures

- **Locator information**
- **HIV counseling**
- **Offer condoms and lubricant**
- **Behavioral assessment**
- **Adherence counseling**

Clinical Procedures

- **Targeted medical history and targeted physical exam, including concomitant medications as well as weight, blood pressure, and pulse data entry to Medidata Rave**
- **ECG**

- **Blood collection**
- **Urine collection for urinalysis**
- **Urine collection for GC/CT testing**
- **Rectal swab for GC/CT testing**
- **Collect any unused blinded oral study product**
- **Dispense OPEN-LABEL oral TDF/FTC pills**

Laboratory Evaluations

- **HIV testing (see SSP Manual)**
- **HCV testing**
- **CBC with differential**
- **Chemistry testing (see Appendix IB)**
- **Liver function testing (see Appendix IB)**
- **Syphilis serologic testing**
- **Urinalysis**
- **Urine GC/CT testing**
- **Rectal swab GC/CT testing**
- **Plasma storage**
- **DBS storage**

Note: If a participant in Step 2 transitions prematurely to Step 3 or misses the Week 153 visit, the procedures listed above will be performed as part of the last visit of Step 2 (whenever that occurs)/Day 0 of Step 3 to the extent possible. All assessments are identical to Week 153/Day 0 listed above with the following exceptions:

- **Behavioral assessment – do not administer if done within the last month before entering Step 3**
- **Acceptability assessment (not listed above) – this should be administered at this visit if it was not done in the last 6 months before entering Step 3**
- **Urine collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3**
- **Rectal swab collection and testing for GC/CT – do not collect/do not perform test if testing occurred within 3 months prior to entering Step 3**
- **Syphilis testing – do not perform test if testing occurred within 3 months prior to entering Step 3**

Revision 26: 5.9 Step 3: Open-label TDF/FTC

This section is revised per # 3 and # 4 under “Summary of Revisions and Rationale” above:

(~~Day 0~~, Weeks 12, 24, 36, 48)

Administrative, Behavioral, and Regulatory Procedures

- **Locator information (Week 48 location information to be collected for reporting of or follow up safety labs/HIV testing after study exit)**
- **HIV counseling**
- **Offer condoms and lubricant**

- ~~Acceptability assessment (Only administer acceptability assessment at week 0 as final assessment if not done in the previous 24 weeks on Step 2)~~
- Behavioral assessment (only at ~~Day 0~~, Weeks 24 and 48; if conducted within the last month before entering Step 3, ~~skip Day 0~~ and conduct at Weeks 12, 24, and 48). **See above regarding Acceptability assessment.**
- Adherence counseling (~~only at Day 0~~, Weeks 12, 24, and 36)

Clinical Procedures

- Targeted medical history and targeted physical exam, including concomitant medications, **as well as weight, blood pressure, and pulse data entry to Medidata Rave**
- Blood collection
- Urine collection for GC/CT testing (~~only at Day 0~~, Weeks 24, 48. ~~Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only~~)
- Rectal swab collection for GC/CT testing (~~only at Day 0~~, Weeks 24, 48. ~~Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only~~) Weeks 24, 48.)
- Dispense pills (~~only at Day 0~~, Weeks 12, 24, 36)

Laboratory Evaluations

- HIV testing (see SSP Manual)
- Chemistry testing (only at Weeks 24 and 48) (see Appendix IC)
- Liver function testing (only at Weeks 24 and 48) (see Appendix IC)
- Syphilis testing (~~only Day 0~~, Weeks 24, 48. ~~Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only~~ at Weeks 24, 48.)
- Urine GC/CT testing (~~only Day 0~~, at Weeks 24, 48. ~~Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only~~)
- Rectal swab GC/CT testing (~~only Day 0~~, Weeks 24, 48. ~~Skip Day 0 if testing occurred within 3 months prior to Day 0, and conduct at Weeks 24 and 48 only~~) at Weeks 24, 48.)
- Plasma storage

Revision 27: 5.10 Visit Windows

The **target** visit windows for all visits, including injection visits, are outlined in the SSP Manual. In brief, the target visit window for injection visits for the Week 5 and 9 injections is +/- 3 days, and is +/- 7 days for all other injections visits. **Visits conducted outside of the target** ~~Broader, allowable~~ visit windows are **allowable without restriction, and are** also defined in the SSP Manual **for scheduling guidance** ~~and are contiguous~~. Each study visit, including the injection visit, should ideally be conducted within the target date range. When that is not possible, visits outside of the target dates ~~and inside the allowable windows~~ may be completed. Additionally, and as already outlined above, the windows for the DXA subset are -30/+ 7 days for Enrollment, and +/- 8 weeks for Weeks 57 and 105.

It is not required to contact the CMC for out of target visit window injection visits provided that they are a minimum of 6 weeks from the last injection and a maximum of 15 weeks from the prior injection, **and for the Week 9 injection, when it is a minimum of 3 weeks from the Week 5 injection and a maximum of 11 weeks from the Week 5 injection.** It is required to contact the CMC for guidance in cases outside of these parameters.

It is not required to contact the CMC for out of target window safety visits no matter when they occur; however, an injection visit may never be completed without a preceding safety visit being completed and all the assessments being resulted and protocol-allowable.

Revision 28: 5.12 Procedures for Participants Who Do Not Complete the Full Course of Injections

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

Participants in Step 1 of the study who are unable to transition to Step 2 of the study for any reason other than HIV infection will be asked to attend annual visits until ~~all participants complete Step 2 of the study~~. **three years from the date of Enrollment.** These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants with confirmed HIV infection during Step 1 of the study will not transition to Step 2 of the study but will be referred for care and will be terminated from the study.

Participants in Step 2 of the study that prematurely stop receiving injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study; **and receive 48 weeks of open label TDF/FTC, (or may be transitioned to Step 3 off study product for safety reasons due to an AE or condition where open label TDF/FTC is contraindicated), followed by annual follow-up until three years from the date of Enrollment (see note below). The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3. If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required.** Once ~~that~~ a participant has completed ~~the required 48 weeks on Step 3~~ **three years of follow-up**, they will then be transitioned to local prevention services ~~and asked to continue to attend annual visits until all participants complete Step 2 of the study, if it is still ongoing at the time of their individual completion of the 48 weeks of open label TDF/FTC provision.~~ These participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study. Participants in Step 2 of the study with confirmed HIV infection will be followed according to Appendix II.

This note is added to refer the reader to Appendix III for additional guidance:

Note: Participants who wish to prematurely discontinue injections in Step 2 due to an injection site reaction AE must follow procedures detailed in Appendix III, Guidance for Injection Site Reactions (ISRs) prior to discontinuation of Step 2 procedures.

The list of procedures is updated to include blood collection as listed in Appendix ID:

For participants that transition to annual visits as outlined above, the following procedures will take place (see also Appendix ID):

- Review/update locator information
- Targeted medical history and targeted physical exam, with concomitant medications update
- HIV pre and post-test counseling
- **Blood collection**

- HIV testing, plasma storage, DBS storage
- Offer condoms and lubricant

Revision 29: 5.13 Planned Unblinding of Study Participants

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

~~When the required number of incident HIV endpoints has been reached, or when~~ **When** the last participant completes scheduled Step 2 follow-up, and when all corresponding procedures at the HPTN SDMC, LC, and LOC have been completed), the study will be unblinded. ~~Participants will move to Step 3 and be unblinded following final confirmation from the HPTN SDMC.~~

Revision 30: 5.14.2 Follow-up (after study Enrollment)

Participants with confirmed HIV infection during Step 2 will not receive additional injections or oral study product, and will be followed per the Schedule of Evaluations and Procedures in Appendix II for approximately 52 weeks, **and will also follow the toxicity management guidelines in Appendix III.** ~~In these cases, the randomized study product assignment will be provided by the HPTN SDMC directly to the participant’s primary care provider.~~ **An Investigator can request unblinding from the HPTN SDMC directly to a participant’s primary care provider in the event a participant becomes infected with HIV during the study; the randomized assignment will not be provided to the site where the participant was enrolled and followed.** See **Section 7.9** and the SSP Manual. In addition, sites will have a standard operating procedure (SOP) that outlines a plan in the event that a participant becomes HIV infected during any Step of the study, and in particular during Step 2 of the study, which must include the participant’s facilitation into locally-available immediate suppressive ART treatment to prevent persistent-monotherapy-related resistance complications for a minimum of 52 weeks post-final injection. The sites will not be responsible for the actual provision/payment of ART. ART or funds for provision of ART will not be provided by the study.

It should be noted that all reactive/positive HIV test results will be reviewed by an independent HIV Endpoint Adjudication Committee whose responsibility is to determine whether the test results meet the primary endpoint of the study of HIV infection.

Revision 31: 5.17 Interim Contacts and Visits **and Missed Visits**

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the investigator or designee at any time during the study.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Interim visits at which no data are collected are not documented on case report forms. Other interim contacts and visits may occur in response to AEs experienced by study participants. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the case report form, and provide or refer the participant to appropriate medical care.

In general, when a visit is missed altogether and a participant reports to the site for the next scheduled visit, the procedures from the missed visit that are not also required for the current visit should be performed.

Refer to the SSP Manual for further details regarding management of such visits.

Revision 32: 5.20 Other Considerations for Premature Transition from Step 2 to Step 3

In other circumstances prompting premature transition from Step 2 to Step 3, if a return to Step 2 blinded study products is feasible and desirable, contact the CMC for guidance on the permissibility and operationalization of such a resumption of blinded study products. For example, a participant may transition prematurely to Step 3 due to relocation to an area where there is no HPTN 083 clinical site; if this participant were to relocate again to an area where there is an HPTN 083 clinical site (including back to the original location), he or she could be considered for a return to Step 2, with resumption of blinded study products, in consultation with the CMC. Protocol-mandated premature transitions to Step 3 for adverse clinical or laboratory events are not eligible for return to Step 2 blinded study products, even if the adverse event has resolved.

Revision 33: 6.4 Expedited Adverse Event Reporting

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the DAIDS Regulatory Support Center (RSC) website at <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids> ~~<http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual>~~.

Revision 34: 6.4.1 Reporting to DAIDS

The DAIDS Adverse Event Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. This form is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting> ~~<http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting>~~. For questions about DAERS, please contact CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

For questions about EAE reporting, please contact the RSC at DAIDSRSCSafetyOffice@tech-res.com.

Revision 35: 6.4.3 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables> ~~http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables~~.

Revision 36: 7.1 Review of Study Design

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

This is a Phase 2b/3 randomized, multi-site, two-arm, double-blinded, double-dummy study of the safety and efficacy of CAB LA vs. TDF/FTC for MSM and TGW. Eligible participants will be randomized 1:1 to receive either oral CAB/CAB LA or matching placebo or daily oral TDF/FTC or matching placebo, and move through 3 steps. Participants will be assigned either active cabotegravir or active TDF/FTC – no participant will receive placebo only. In Step 1, study participants will receive oral tablets for 5 weeks, followed by entering Step 2 and undergoing a single injection at two time points 4 weeks apart and every 8 weeks thereafter and daily oral tablets ~~until the required number of incident HIV endpoints is accrued (172), estimated to be when the final participant reaches 60 weeks on Step 2 (week 65 for the final participant)~~ **for a total of 3 years**. In Step 3, all participants will receive open-label daily oral TDF/FTC for up to 48 weeks. Participants will therefore be followed ~~between 113 weeks to 233 weeks (between 65 and 185 weeks~~ **for 3 years** on blinded study ~~medication-product~~ **medication-product** and ~~up to 48 weeks~~ on open-label daily oral TDF/FTC). All participants will transition to local HIV prevention services after their completion of Step 3.

Revision 37: 7.5.2 Secondary Endpoints

This section is revised per # 4 under “Summary of Revisions and Rationale” above:

- **Weight, blood pressure, pulse, fasting glucose, and fasting lipids**

Revision 38: 7.6 Sample Size and Interim Monitoring

Only the paragraphs impacted are depicted here:

Assuming CAB LA is 25% more effective than TDF/FTC, approximately 174 observed HIV-infections will provide 90% power to rule out a non-inferiority margin of HR=1.23, with type-I error $\alpha = 0.025$ (see Figure 7 below). This non-inferiority margin is an M2 margin based on an inverse-variance weighted meta-analysis of three randomized controlled trials of TDF/FTC versus placebo in MSM: iPrex, iPERGAY, and PROUD4, 35-36. The M2 margin is defined as the reduced bound that is designed to preserve a clinically acceptable amount of the benefit provided by the active control (TDF/FTC). Setting M2 to be 50% of M1 (on the log scale in the case of hazard ratios) is considered to be conservative. M1 is defined as the lower limit of the 95% confidence interval around the placebo versus active-control HR estimate (1.39, based on the meta-analysis). Once the stated number of HIV-

infections have been observed, non-inferiority will be established if the estimated CAB LA versus TDF/FTC hazard ratio point estimate is approximately 0.90 or less (indicating a 10% or better advantage of CAB LA over TDF/FTC), and superiority will be established if the hazard ratio point estimate is approximately ~~0.68~~ **0.74** or less (indicating a ~~32%~~ **26%** or better advantage of CAB LA over TDF/FTC). The power to detect superiority is 47%.

The number of enrolled participants needed to observe the target number of HIV-infections depends on the background HIV incidence in the study populations, the efficacy of CAB LA and TDF/FTC in these populations, the dropout rate, and the study duration. Assuming (a) annual HIV incidence for the TDF/FTC arm is 2.0% (similar to the 1.8% incidence observed in the iPrex OLE study); (b) CAB LA is 25% more protective than TDF/FTC; and (c) the annual dropout rate is 7.5%, then approximately ~~4500~~ **5000** individuals will be needed to enroll and be followed for an average of 2.5 years. See Figure 8 below.

Revision 39: 7.7 Accrual and Retention

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

~~A total of 4500~~ **Approximately 5000** participants will be enrolled in approximately ~~30 months~~ **3.5 years** and followed for ~~an a maximum~~ average of ~~2.5~~ **3.0** years **on blinded study product, followed by 1 year on open-label study product, for a total of a maximum of 4.0 years of follow-up.** An average annual retention rate of at least 92.5% percent will be targeted.

Revision 40: 7.9 Blinding

This section is revised per # 3 under “Summary of Revisions and Rationale” above:

Study site staff, with the exception of the site Pharmacist of Record or their designee, and participants will be blinded to the random assignments. Blinding will be maintained until the trial is completed or stopped, i.e., the trial is stopped early, or the ~~last participant enrolled in to Step 2 completes~~ ~~approximately 60 weeks of follow-up or the~~ required number of endpoints or person years has been met. At a specified time directed by the HPTN SDMC, participants will be notified of their treatment assignment. In addition, as noted in Section 5.13.2, an Investigator can request unblinding to the HPTN SDMC in the event that a participant becomes infected with HIV during the study, and the SDMC will assist in directly providing the participant’s primary health care provider the randomized arm assignment information per their SOP; the randomized assignment will not be provided to the site where the participant was enrolled and followed.

Revision 41: 7.11.3 Analyses of Secondary Objectives

This section is revised per # 4 under “Summary of Revisions and Rationale” above:

- **To compare changes in weight, blood pressure, pulse, fasting glucose, and fasting lipids among participants receiving oral CAB/CAB LA vs. oral TDF/FTC**

Change from baseline (enrollment) for weight, blood pressure, pulse, fasting glucose, and fasting lipids will be computed at each follow-up visit where these measures are collected. The mean changes will be plotted over time by treatment arm for visits where participants remained on blinded, protocol-specified treatment. (Per-protocol analysis). A linear mixed model will be fit with categorical intervals for time in study, treatment and time by treatment interaction to evaluate time trends in each arm and the association between treatment and biological measures. Categorical models will also be used to assess changes over time in BMI category, proportion of participants with 5% or more weight change, and occurrence of new diabetes diagnoses. Differences in time trends and treatment effects will be explored for demographic and clinical subgroups, including race/ethnicity, age, baseline smoking status, baseline BMI, and baseline weight.

Revision 42: 7.11.4 Analyses of Tertiary Objectives

This section is revised to remove India:

The Cost-effectiveness of Preventing AIDS Complication-US and International models (CEPAC I), will be used and populated with data specific for each of the countries -- US, Brazil, **and** South Africa ~~and India~~. The model will be updated, specified, programmed and debugged for simulations specific to this protocol. It will further be parameterized with efficacy and resource utilization data obtained from the trial. We will use total cohort data where there are not statistically significant differences between country-level data. We will use country-specific data where those difference occur. For each country, the model will have the capacity to generate outcomes including: 1-, 5-, 10-year survival, life expectancy, per person lifetime costs (and a breakdown of where those costs occurred), 1- and 5- year budgetary impact, as well as incremental cost-effectiveness. This will allow for comparison of cost-effectiveness outcomes across regions of analysis with differences in baseline incidence, costing structures and gross domestic products (willingness/ability to pay).

Revision 43: 8.6 Study Discontinuation

This section is revised to add ethics committees:

The study also may be discontinued at any time by NIAID, the HPTN, the pharmaceutical sponsors, the US FDA, other government or regulatory authorities (OHRP), or site IRBs/ECs.

Revision 44: 10.1 Protocol Registration

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at <https://rsc.niaid.nih.gov/clinical-research-sites/protocol-registration> <http://rsc.tech-res.com/protocolregistration/>.

Revision 45: 10.6 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. In accordance with Federal regulations, for each of the investigational products tested, the Investigator will retain all study records for at least two years following the date of marketing approval for the study product for the indication in which it was studied: **and at least three years after the completion of research.** If no marketing application is filed, or if the application is not approved, the records must be retained for two years after the US FDA is notified that the IND is discontinued. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

Completion of a clinical research study occurs when the following activities have been completed:

- **All research-related interventions or interactions with human subjects (e.g. when all subjects are off study);**
- **All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;**
- **All analysis of identifiable private information described in the IRB/EC-approved research plan;**
- **Primary analysis of either identifiable private or de-identified information.**

Revision 46: References

Three new references have been added (references 86, 87, and 88). The website address for reference 67 has been updated. Additionally, references have been renumbered in the protocol document and the corresponding reference list due to numbering errors identified.

Revision 47: Appendix IA: Schedule of Procedures and Evaluations – Screening; Step 1 – Blinded Daily Oral Pills

This section is revised per # 4 under “Summary of Revisions and Rationale” above (Only the revised table is shown below):

	Screening	Step 1		
		DAY 0/Enrollment	WEEK 2	WEEK 4
ADMINISTRATIVE, BEHAVIORAL, REGULATORY				
Informed consent	X			
SexPro assessment (US sites only for inclusion; South American sites only for data collection)	X			
Locator information	X	X	X	X
Demographic information		X		
Randomization		X		
HIV counseling	X	X	X	X
Offer condoms and lubricant	X	X	X	X
Baseline acceptability assessment		X		
Baseline behavioral assessment		X		
Adherence counseling/pill count (Pill count Week 2 and 4 only)		X	X	X
CLINICAL EVALUATIONS & PROCEDURES				
History (including bleeding history at Screening), con meds, physical exam	X	X	X	X
Height ⁷ , weight, blood pressure, pulse data entry to Medidata Rave		X	X	X
ECG (screening ECG can serve as baseline value)	X			
DXA (BMD subset only, 175 per arm), to include dietary calcium and Vitamin D assessment		X		
Blood collection	X	X	X	X
Urine collection for urinalysis		X		
Urine collection for urinalysis GC/CT testing		X		
Rectal swab for GC/CT testing ¹		X		
Dispense Pills (enough for 5 weeks)		X		
LOCAL LABORATORY EVALUATIONS & PROCEDURES				
HIV testing ²	X	X	X	X
HBV and HCV testing ³	X	X		
CBC with differential	X	X	X	X
Chemistry testing ⁴	X	X	X	X

	Screening	Step 1		
		DAY 0/Enrollment	WEEK 2	WEEK 4
Liver function tests ⁵	X	X	X	X
Fasting glucose and fasting lipid profile ⁶		X		
Syphilis serologic testing		X		
BMD subset only: 25-OH-Vitamin D		X		
Urine GC/CT testing		X		
Rectal swab GC/CT testing ¹		X		
Urinalysis (protein and glucose)		X		
Plasma storage	X	X	X	X
DBS storage				X
Whole blood storage		X		

FOOTNOTES FOR APPENDIX IA

¹ If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

² The HIV testing algorithm is provided in **Appendices IE-G** and the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

³ HBsAg and HCV antibody testing are required at Screening. At Enrollment, HBsAb and HBcAb required; no HCV testing required at Enrollment.

⁴ Creatinine required at screening; at and after enrollment, BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase are required.

⁵ ALT and bilirubin required at screening; at and after enrollment, AST, ALT, total bilirubin, and alkaline phosphatase are required.

⁶ 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.

⁷ **Height is a one-time measurement required to be captured in the source documents at enrollment as part of the complete physical exam. The height measurement should be entered into MediData Rave when the database is updated to capture the measurement.**

Revision 49: Appendix IC: Schedule of Procedures and Evaluations - Step 3 – Open Label Daily Oral TDF/FTC Post-Last Injection

This section is revised per # 3 and # 4 under “Summary of Revisions and Rationale” above (Only the revised table is shown below):

Procedures	Week 153/ Day0*	Week 12	Week 24	Week 36	Week 48
ADMINISTRATIVE, BEHAVIORAL, REGULATORY					
Locator Information	X	X	X	X	X
HIV Counseling	X	X	X	X	X
Offer Condoms and lubricant	X	X	X	X	X
Acceptability Assessment ²	X				
Behavioral Assessment (if done in last 4 weeks, skip D0 and start at W12)	X		X		X
Adherence Counseling	X	X	X	X	
CLINICAL EVALUATIONS & PROCEDURES					
History, concomitant medications, physical exam	X	X	X	X	X
Weight, blood pressure, pulse data entry to Medidata Rave	X	X	X	X	X
Blood Collection	X	X	X	X	X
Urine collection for GC/CT testing	X ¹		X		X
Rectal swab for GC/CT testing ³	X ¹		X		X
Dispense pills	X	X	X	X	
LOCAL LABORATORY EVALUATIONS & PROCEDURES					
HIV testing ⁴	X	X	X	X	X
Chemistry testing ⁵			X		X
Liver function tests ⁶			X		X
Syphilis serologic testing	X ¹		X		X
Urine GC/CT testing	X ¹		X		X
Rectal swab GC/CT testing	X ¹		X		X
Plasma storage	X	X	X	X	X

FOOTNOTES FOR APPENDIX IC

* Day 0 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.*For participants who transition to Step 3 prematurely, the timeline for Day 0 begins 8 weeks after that participant’s last injection, even if the participant does not report to the Day 0 visit (or the Week 12 visit, etc.). The timeline for Step 3 continues whether or not a participant attends visits. Sites may contact the CMC for questions regarding participants who transition to Step 3 prematurely who are then subsequently missing, though it is not required to do so. For participants who transition to Step 3 at Week 153, the first day of Step 3 begins at Week 153 and is considered Day 0 of Step 3.

¹ Skip Day 0 if testing has occurred within last 3 months of Day 0, and do only at Weeks 24 and 48.

²Administer acceptability assessment at ~~week~~ **Day 0** as final assessment if not done in the previous ~~24 weeks~~ **6 months** on ~~S~~step 2, to include a brief preference assessment

³ If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

⁴ The HIV testing algorithm is provided in **Appendices IE-G and** the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

⁵ Required chemistry testing: BUN/Urea, creatinine, CPK, calcium, phosphorous, glucose, amylase, and lipase.

⁶ Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.⁶ Required LFTs: AST, ALT, total bilirubin, and alkaline phosphatase.

Revision 50: Appendix ID: Schedule of Procedures and Evaluations for Annual Visits

This section is revised per # 3 under “Summary of Revisions and Rationale” above. Only the first two bullets in this Appendix are depicted below:

The procedures listed below are for the following participants:

- Participants in Step 1 who do not transition to Step 2 for any reason other than HIV infection will be asked to attend annual visits until ~~all participants complete Step 2 of the study~~ **three years from the date of Enrollment.**
- Participants in Step 2 who prematurely stop receiving injections for any reason other than HIV infection will transition to Step 3, complete the required 48 weeks of follow-up in Step 3, and will then be asked to attend annual visits until ~~all participants complete~~ **three years from the date of Enrollment. The timepoint during Step 2 of the study, that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3. If the completion of open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required.**

Revision 51: Appendix III: Guidance on Toxicity Management for Specified Toxicities: ALT

This section has multiple revisions per # 3 under “Summary of Revisions and Rationale” above. Additional revisions have been made, only the items impacted in Appendix III are depicted below:

Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually until ~~all participants complete Step 2 of the study.~~ **three years from the date of Enrollment.** All such cases must be reported to the CMC.

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in ALT		
Grade 2 and higher		<p>Oral phase (Step 1): A Grade 2 ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, should be confirmed within one week. Oral study drug may continue until the confirmatory results are available; no injections should be administered until confirmatory results are available during consideration of the Week 4 ALT value. If the repeat value is \leq Grade 2 at Week 2, study drug may continue to Week 4. If the repeat value is $<$ Grade 2 at Week 4, the participant may proceed to Step 2 injection phase. If the repeat value is Grade 2 or higher at Week 4, study product should be stopped, and the participant will be followed annually until all participants complete Step 2 of the study three years from the date of Enrollment. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>A Grade 3 or higher ALT abnormality reported at Week 2 or Week 4, regardless of relatedness to the study product, will prohibit a participant from entering the injection phase of the study, and the participant will be followed annually until all participants complete Step 2 of the study three years from the date of Enrollment. All such cases must be reported to the CMC. In addition, participants will be followed with weekly ALT assessments until they return to \leq Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product and the participant will be followed annually until all participants complete Step 2 of the study three years from the date of Enrollment. All such cases must be reported to the CMC.</p>

CONDITION AND SEVERITY ¹	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT ²
ELEVATIONS in ALT		
Grade 2 and higher		<p><u>Injection phase (Step 2):</u> The CMC should be notified as soon as possible. For a Grade 2 ALT, the CMC will determine whether further injections may be given in cases where levels are ≤ Grade 2 prior to the next scheduled injection. Unless otherwise specified by the CMC, for Grade 2 ALT, repeat testing should be performed weekly until levels are ≤ Grade 1. For Grade 3 and higher ALT, study product will be permanently discontinued. For Grade 3 and 4 ALT, repeat testing should be performed as soon as possible, and participants should be followed weekly until levels are ≤ Grade 1. If an etiology for elevated ALT is identified or persistent without explanation, the CMC may direct an alternate interval for follow-up.</p> <p>Participants who are permanently discontinued from study product should continue to be followed on study/off study product, following the Step 3 Schedule of Evaluations for Arm A.</p> <p>Note the following for cases of exercise-induced CK abnormalities: Cases of CK abnormality, presumed to be exercise induced, at the Grade 3 or higher level accompanied by ALT abnormalities of Grade 3 or lower up to and including Grade 3 should be brought to the attention of the CMC for adjudication of further management and further administration of study product. Grade 4 elevations in ALT, regardless of CK elevation will prompt permanent discontinuation of study product. If the participant is in Step 1 of the study when this occurs, study product will be discontinued and the participant will be followed annually until all participants complete Step 2 of the study, If the participant is in Step 2 when this occur, the participant will</p> <p><u>Open-label phase (Step 3):</u> Participants outlined above who transition to Step 3, off the study product, follow will be followed per the Schedule of Procedures and Evaluations for Step 3 except for provision of study product.</p> <p>When Step 3 concludes in these cases, the participant will be followed annually until all participants complete three years from the date of Enrollment. The timepoint during Step 2 that a participant transitions to Step 3 will determine whether they will be asked to attend annual visits following the completion of Step 3 2. If the completion of the study-open label TDF/FTC for Step 3 post-dates three years from the date of Enrollment, no further annual follow-up is required. All such cases must be reported to the CMC.</p>

Revision 52: Appendix III: Toxicity Management - Guidance on Toxicity Management for Specified Toxicities:

Only the Note under Creatinine Clearance is depicted below:

Creatinine Clearance

NOTE: Adverse events related to creatinine clearance should be based on examination of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Enrollment/ Visit 2.0). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF. Clinical Management of Grade 3 and Grade 4 changes in creatinine clearance should follow the “Toxicity Management General Guidance” ONLY when the absolute creatinine clearance is < 90 mL/min. That is, changes in creatinine clearance of >30% from baseline that DO NOT result in an absolute creatinine clearance < 90 mL/min do NOT need to be reported to the CMC or more frequent clinical monitoring. **Additionally, changes in creatinine clearance of > 30% that are accompanied by a creatinine that remains within normal limits also do not need to be reported to the CMC and do not require more frequent clinical monitoring.**

Revision 53: Appendix III: Toxicity Management - Guidance for Injection Site Reactions (ISRs)

The CMC must be informed of all Grade 3 or 4 ISRs to determine etiology and assess appropriate continued study participation. ISR discomfort can be managed symptomatically (e.g. cold/warm compress, acetaminophen, ibuprofen) if the reaction is interfering with the participant’s ability to perform activities of daily living. **Starting at the point of when Version 3.0 is implemented at an individual site, sites should document all interventions that have been attempted to mitigate injection site reactions, which should include at a minimum:**

- 1. Pre-treatment (prior to injection administration) warm compresses**
- 2. Topical or oral pre-treatment with NSAID preparations, unless contraindicated**
- 3. Immediate post-injection massage to injection location**
- 4. Post-treatment warm or cold compresses**
- 5. Post-treatment NSAID or other analgesic preparations, topically or orally**

Such interventions and their outcome should be documented in the source documents and the CMC consulted prior to discontinuation of Step 2 follow-up. A proactive and comprehensive approach to mitigating ISRs should be undertaken, with premature transition from Step 2 to Step 3 being reserved for refractory cases in extreme circumstances.

Revision 54: Appendix IV: Sample Screening and Enrollment Informed Consent Form

The sections of the sample informed consent impacted by changes to the protocol per # 3 under “Summary of Revisions and Rationale” above are depicted below. The sections are outlined for ease of reference:

Cover page:

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version 23.0

July 25, 2018

October 31, 2019

DAIDS Document ID: 20725

The general overview was updated with the revised study size, as well as typographical corrections:

This study is being offered to **approximately 4500-5000** HIV-uninfected men who have sex with men (MSM) and transgender women (TGW) that have sex with men in Asia, North and South America, and South Africa. Before you decide whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

A description of this ~~study~~ **clinical trial** will be available on **http://www.ClinicalTrials.gov**, as required by ~~US-U.S.~~ Law. This ~~w~~Web site will not include information that can identify you. At most, the ~~w~~Web site will include a summary of the results. You can search this ~~w~~Web site at any time.

The study group section was updated to reflect the revised study size and revised length of follow-up:

If you decide to be in this study, you will be placed in to 1 of 2 groups. Each group will have ~~2250~~ **approximately 2500** people in it. ~~We do not know exactly how long this study will last because the length of the study is determined by when you join the study and how well people do on the study. Your participation in the study could last up to 4 years and a half~~ **You will be followed for approximately four** years, and include up to ~~57 visits~~ **approximately 47 visits** to this clinic over that time. ~~As the study goes on, we will let you know about the study progress and plans for how long it will be.~~

Group A – this group gets real CAB pills and injections:

- Step 1: Real CAB pill AND placebo pill for TDF/FTC (2 pills total) every day for 5 weeks
- Step 2: Real CAB injections given as one shot, then another shot a month later, and then every 2 months after that AND placebo pill for TDF/FTC every day up to three ~~and half~~ years **after enrollment**

- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

Group B – this group gets real TDF/FTC pills:

- Step 1: Real TDF/FTC pill AND placebo pill for CAB (2 pills total) every day for 5 weeks
- Step 2: Placebo CAB injection AND real TDF/FTC pill everyday up to three ~~and a half~~ years **after enrollment**
- Step 3: Real TDF/FTC pill every day for about a year, then move to local HIV prevention services

In Step 1, everyone starts the study by taking pills for 5 weeks. This is to see if you have any serious side effects to the study drugs before you start getting the shots.

In Step 2, everyone takes pills and gets shots. This step will ~~last up to~~ **continue until** three ~~and a half~~ years, ~~depending on when you started in the study~~ **after enrollment**.

In Step 3, **which starts on the same day as the last day of Step 2**, everyone gets the real TDF/FTC every day for about a year, then your participation in the study will end and we will refer you to local HIV prevention services. There are no current plans for the study to offer the injectable CAB drug to study participants after the completion of the study.

Step 1 enrollment visit section is updated to include pulse in metabolic measures:

- Give you a complete physical exam, to include measuring your height, weight, ~~temperature,~~ blood pressure, **pulse**, and ask you about any other medicines you are taking.

Step 1 weeks 2 and 4 visits section is updated to list metabolic measures and also to reflect the revised length of follow-up:

- Give you a brief physical exam, **to include measuring your weight, blood pressure, pulse, and** ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.

If you have a side effect from the pills, or if you do not take enough of your pills, you may not be able to get the shots. If this happens, we will ask you to attend a visit once a year ~~until all participants for three~~ **years from the time you enrolled** in the study ~~have completed Step 2~~. The procedures for those visits are outlined later in this consent form document [sites may also list the procedures here].

Step 2 week 5 visit section is updated to list metabolic measures:

- Give you a brief physical exam, **to include measuring your weight, blood pressure, pulse,** ask you if you have experienced any side effects from the study drugs, and ask you about any other medicines you are taking.

Step 2 injection visits section is updated to reflect revisions to the revised length of follow-up, to list metabolic measures, and to include collection of unused oral study product at the conclusion of Step 2:

Step 2: All other visits where injections occurs: Week 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, ~~161, 169, 177, 185~~ (**an injection is not given at Week 153 but is a study visit**),

In this step of the study, there will be approximately ~~23 visits~~ **19 visits** where you will receive a shot and study pills. Injections will be given approximately every 2 months (8 weeks) after the first two are given one month (4 weeks) apart. These visits will last up to XX hours. During these visits, the study staff will:

- Give you a brief physical exam, **to include measuring your weight, blood pressure, pulse**. Ask you if you have experience any side effects from the shots you received, and ask you about any other medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for:
 - HIV testing, to check your general health, the health of your liver, and for storage (every injection visit)
 - HCV testing about every year (Weeks 57, 105 and 153 only)
 - Syphilis testing about every 6 months throughout Step 2 (Weeks 33, 57, 81, 105, 129, ~~153~~ and ~~177~~**153** only)
 - Testing to see how much cholesterol is in your blood two times during the study, one year apart (Weeks 57 and 105 only). For the cholesterol test, you will be instructed to not eat or drink anything other than what the study staff tell you is acceptable for 8-12 hours before your blood is drawn.
- Collect a urine sample to see if there is sugar or protein in your urine about every year for 3 years (Weeks 57, 105, and 153 only).
- Ask you to answer questions about your sexual behavior at every injection visit for about 2 years, and then every other injection visit for the rest of Step 2 (Weeks 5, 9, 17, 25, 33, 41, 49, 57, 65, 73, 81, 89, 97, 105, 121, 137, 153, ~~169, 185~~ only)
- Ask you questions about how you feel about taking pills and getting injections about every 6 months for two years and then once more a year later (Weeks 17, 41, 65, 89, **and** 137 ~~and 185~~).
- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia about every 6 months throughout Step 2 (Weeks 33, 57, 81, 105, 129, ~~153~~ and ~~177~~**153** only).
- Give you your study pills, and explain how to take them, and any side effects they may cause (at all injections visits).
- **At Week 153 only or if you move to Step 3 early, collect any unused blinded oral study product**
- Give you a shot (at all injection visits)- **except for Week 153**).

Post-injection visits section is updated to reflect the revised length of follow-up:

Step 2: Post-Injection Visits: Weeks 6, 10, 19, 27, 35, 43, 51, 59, 67, 75, 83, 91, 99, 107, 115, 123, 131, 139, 147, ~~155, 163, 171, 179, 187~~)

[Note: Sites may remove Week numbers in the text below if easier to depict it in a table or refer to the Schedule of Procedures and Evaluations].

There will be up to approximately ~~24~~ **19** visits following each visit where you got a shot. These visits will last up to XX hours. During these visits, the study staff will:

Step 3 visit section is updated to reflect the revised length of follow-up and to include metabolic measures:

Step 3: If you stopped getting injections early, you will go to Step 3. If you got all of your injections, you will go to Step 3: **at Week 153 of Step 2, which is the same visit as Day 0 of Step 3.** This step includes ~~5~~ **4 more** visits over about a year (Week 0, 12, 24, 36, and 48).

Each visit will last up to XX hours. During these visits, the study staff will:

- Give you a brief physical exam, **to include measuring your weight, blood pressure, pulse,** and ask you about any other medicines you are taking
- Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing, to check your general health, the health of your liver, the amount of the study drug in your blood, and for storage. Note: Blood will be collected for syphilis testing at Day 0, (**which is the same as Step 2 Week 153**), and Weeks 24 and 48. However, if you have had syphilis testing within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48.
- Perform a swab of your rectum and collect urine for gonorrhea and chlamydia (Day 0 (**same as Step 2 Week 153**), Week 24 and 48 only). If you have had this test within 3 months of joining this part of the study, you will only have this done at Week 24 and Week 48 only.

If you moved into Step 3 prematurely, some of the procedures above may not have to be performed, which will depend on when during the study you moved into Step 3. The procedures that may not have to be performed are asking you about questions about your sexual behavior, urine collection and testing for GC/CT, rectal swab collection and testing for GC/CT and syphilis testing.

Annual visits section is updated to reflect the revised length of follow-up and to include collection of any unused oral study product at the conclusion of study participation:

Annual Visits

Procedures for HIV testing every year if you do not get shots or have completed or been in Step 3:

As we mentioned, the study begins with taking pills only for five weeks before you can start with the shots. During this time, you may get a side effect that would result in not moving to the part of the study where the shots are given. Or, you may not have taken enough of the pills. If any of this happens, you would not get shots, and we would ask you to attend a visit once a year ~~while Step 2~~ **until three years from your date** of ~~the study is still ongoing~~ **Enrollment** in order to test you for HIV.

If you do get shots but stop getting them early, you will move to Step 3 of the study where you will get real TDF/FTC for approximately a year and come in for visits every three months for approximately a year. After that time, we will help you find prevention services in the local area, and we will ask you to attend a visit once a year ~~while Step 2~~ **until three years from your date** of ~~the study is still ongoing~~ **Enrollment** in order to test you for HIV.

As we mentioned at the beginning of the consent form, you can decide to not participate in the study at any time during the study. If you decide this during a study visit, that study visit may be your last study visit. If you decide this in between visits, we will ask you to return any unused study pills.

A new risk is added to the RISKS AND/OR DISCOMFORTS section:

Possible Injection Side Effects:

The injections will be given in the muscles of your buttocks (bottom “cheeks”). The injection could be given too deeply or not deeply enough, missing the muscle and entering your skin, blood, or a nerve. The risk of this is unknown but may result in higher levels of the injected medication in your system. Getting injections could also cause some people to feel lightheaded or feel like they might pass out, or ‘faint’. This reaction, called a ‘vasovagal reaction’, can occur with many medical procedures and resolves quickly.

Signature page is updated for Version 3.0:

SIGNATURE PAGE

HPTN 083

A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Version 2 **3.0**

~~July 25, 2018~~

October 31, 2019