

Letter of Amendment #3 to:

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 4.0, February 10, 2021

**DAIDS Document ID: 20725
IND # 122, 744**

FINAL Version of LoA #3: December 01, 2021

The information contained in this Letter of Amendment (LoA) must be submitted to site Institutional Review Boards (IRBs) and/or Ethics Committees (ECs) as soon as possible for their review and approval. Approval must also be obtained from site regulatory entities if applicable per the policies and procedures of the regulatory entities. All IRB/EC and regulatory entity requirements must be followed.

LoA #3, dated December 01, 2021, corrects omissions to the consent form changes made in LoA #2, dated November 02, 2021, to Version 4.0. LoA #2 has been withdrawn. Therefore, LoA #2 will not be implemented and LoA #3 replaces LoA #2 in full. All items included in LoA #2 are repeated in LoA #3, with the addition of the consent corrections. Sites must implement the content of this LoA upon receiving IRB/EC/other applicable regulatory entities approval (unless still operating under Version 3.0 of the protocol). Sites also must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC) (sites do not have to wait for PRO registration in order to implement the LoA). Sites will receive a registration notification for the LoA after the DAIDS PRO verifies that all required registration documents have been received and are complete.

Please file this LoA, corresponding site-specific informed consent forms, all associated IRB/EC and regulatory entity correspondence, and all correspondence with the DAIDS PRO in your essential documents files for HPTN 083.

If the HPTN 083 protocol is fully amended in the future, this Letter of Amendment will be incorporated into the next version. Text appearing below in highlighted **bold** will be added, and text appearing in highlighted **strike-through** will be deleted.

Rationale of Revisions and Implementation

1. A Protocol Signature Page is added per this LoA.

See next page

Protocol 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

DAIDS Document ID # 20725

Version 4.0

February 10, 2021

Letter of Amendment #3, December 01, 2021

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

2. List of Abbreviations and Acronyms

Body mass index and open label extension are added. Only the new text is included below:

BMI **body mass index**

OLE **open label extension**

3. Protocol Team Roster

David Margolis is removed; Yoshihiko Murata is added.

David Margolis, MD, MPH

ViiV Healthcare

5 Moore Drive

Durham NC, 27709

Phone: 919-483-7869

Fax: 919-315-6359

Email: david.a.margolis@viivhealthcare.com

Yoshihiko Murata, MD, PhD

ViiV Healthcare

5 Moore Drive

Durham NC, 27709

Phone: 919-717-2621

Email: yoshihiko.x.murata@viivhealthcare.com

4. Section 7.8, Random Assignment

Race and ethnicity are removed from randomization stratification parameters. Only the impacted portion of this section is depicted:

Enrolled participants will be randomized to one of two study arms in a 1:1 ratio. Randomization will be stratified by study site, **race, and ethnicity**, and a permuted blocks design will be used to ensure balanced treatment assignments within study site.

5. Appendix V, Part A, Section 3, Description of Steps 4 and 5

Additional guidance is added for consenting participants who are ineligible or unwilling to participate in the open-label extension (OLE) under Version 4.0 of the protocol. Sites are required to provide new information and consent to all participants within six months of receiving Version 4.0 implementation notification. Only the impacted portions of this section are depicted:

Participants originally randomized to TDF/FTC who have passed three years from the date of enrollment will not be permitted to make the choice of entering Step 5 (open-label TDF/FTC), per the original study design and informed consent; such participants will be referred to local standard of care for prevention services. **These participants, as well as other participants who are otherwise not eligible to join the open-label extension (OLE) or who do not wish to participate in the OLE, will still be consented to Version 4.0 so that they may receive the new information about cabotegravir contained in the Version 4.0 consent form, and to document that they will not take part in the OLE. As outlined in the consent form, participants who leave the study before their last scheduled study visit will be asked to complete a final visit based on the Version 4.0 schedule if available to do so. Participants who do not participate in the OLE will be told that this will be considered their final study visit and will be asked to complete the procedures listed for participants who are not continuing under Version 4.0.**

All participants who wish to continue study participation under Version 4.0 must be consented within six months of HPTN LOC notification to the site to begin implementation of Version 4.0. Participants will not be allowed to transition to the OLE beyond six months from date of HPTN LOC notification to implement Version 4.0. This includes participants who have indicated that they need time to decide whether they want to participate in the OLE. If a participant returns to a site more than six months after LOC notification to implement Version 4.0, the participant will be provided the new information in the informed consent form and will mark not eligible to participate on the Version 4.0 consent signature page.

Contact the CMC for guidance for other cases that do not fit ~~this description~~ **the descriptions** or the criteria **described** above.

6. Appendix V, Part A, Section 4, Open-Label Extension Objectives/Endpoints/Statistical Analysis

Part A, Section 4 is a new section to add the open-label extension study objectives, study endpoints and the corresponding statistical analyses in Version 4.0 of the protocol:

Open-Label Extension Objectives/Endpoints/Statistical Analysis

Objectives

- 1. To estimate HIV incidence in participants who receive CAB during the unblinded and OLE periods, both separately and in aggregate; compare these outcomes to HIV incidence in the CAB-LA arm during the blinded period.**
- 2. Evaluate the safety of CAB during the unblinded and OLE periods; compare these outcomes to safety during the blinded period.**
- 3. Estimate HIV incidence in participants who choose to receive TDF/FTC during the OLE period, separately and in combination with incidence during the unblinded period among those randomized to TDF/FTC. Compare with HIV incidence during the blinded period in those randomized to TDF/FTC.**

4. Evaluate safety and HIV incidence among participants randomized to CAB-LA who receive TDF/FTC dosing during temporary discontinuation of CAB injections (e.g. due to lack of access during COVID, or between the end of randomized dosing and restart of CAB-LA during OLE).
5. Summarize PrEP choice at entry into OLE according to randomized study arm and most recent study product, including the number/proportion of participants who fall into each of the following (a) CAB-arm: continue on CAB, (b) CAB-arm: switch from CAB to TDF/FTC at entry into OLE, (c) CAB-arm: switch back from TDF/FTC to CAB at entry into OLE, (d) CAB-arm: stay on TDF/FTC, (e) TDF/FTC-arm: switch to CAB, and (f) TDF/FTC-arm: remain on TDF/FTC. And, among those initially assigned to TDF/FTC who choose to initiate CAB during the OLE, how many elect oral lead in and how many choose direct to inject.
6. Assess CAB continuation, adherence, and acceptability during the OLE and unblinded periods compared to the blinded period.
7. Assess tail-phase HIV incidence rates amongst those who discontinue CAB-LA injections
8. Characterize HIV infections, including drug resistance, drug concentrations, viral load, and results from HIV diagnostic tests
9. Evaluate weight changes over time among participants who transition from TDF/FTC to CAB during the OLE, and among participants who transition from CAB to TDF/FTC.
10. STI incidence rates to corroborate/contextualize HIV incidence rates as a biomarker of risk behavior
11. Summarize reasons for choice/preferences for study product.

Exploratory Objectives

1. To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection, hepatitis infection, or STIs; antiretroviral (ARV) drug use; pharmacogenomics; further characterization of HIV infections; and evaluation of laboratory assays related to the study objectives
2. To continue to explore possible drug-drug interactions between cross-sex hormone therapy (csHT) and cabotegravir and TDF/FTC in a subset of participants who self-identify as transgender women.
3. Consider extending the CAB case-control (concentration-response) analysis to include infections that occur in persons who received CAB-LA during the unblinded and/or OLE phase of the study.

Endpoints

1. Number of incident HIV infections among participants who receive any CAB dosing, oral or injectable, during the unblinded stage and the OLE period, as well as infections that occurred during the 48-week CAB tail phase following CAB LA discontinuation.

2. Grade 2 and higher clinical or laboratory adverse events (AEs). Grade 1 and higher injection site reactions.
3. Number of incident HIV infections among participants who are initially randomized to TDF/FTC (blinded and unblinded) and any participants who choose to receive TDF/FTC during OLE follow-up.
4. Number of documented incident HIV infections, and grade 2 or higher AEs, among participants receiving temporary TDF/FTC during temporary discontinuations of CAB.
5. Treatment choice at entry into the OLE.
6. Time of CAB discontinuation during the OLE and unblinded stages.
7. Number of documented incident HIV infections between 8 and 56 weeks after the last CAB injection.
8. Genotypic resistance, drug concentrations, infection timing, and HIV testing results for all incident infections. Phenotypic INSTI resistance may also be evaluated in selected cases.
9. Weight and body mass index (BMI) among participants who transition to or from CAB.
10. Number of STIs detected among participants during the unblinded and OLE periods.
11. Self-reported reasons for choice/preferences for study products.

Statistical Analysis

1. To estimate HIV incidence in participants who receive CAB during the unblinded and OLE periods, both separately and in aggregate. Compare against HIV incidence in the CAB-LA arm during the blinded period.
 - a. The first-positive date for incident HIV events will be determined by an independent Endpoint Adjudication Committee (EAC); the infection time will be calculated as the midpoint between the first HIV positive visit date and the last HIV negative visit date.
 - b. Overall incidence. Incident HIV events will be classified as having occurred in the blinded or OLE periods based on the infection time and participant-specific dates of unbinding and entry into the OLE. A “participant who received CAB” in blinded follow-up will be defined as being randomized to CAB-LA; in unblinded follow-up as having received at least one pill or injection; and in OLE follow-up as having received at least one pill or injection. Person time starting with last visit prior to May 14th, 2020 up through the first OLE visit will be classified as “unblinded” time; person time following entry into the OLE will be classified as “OLE” time. Incidence rates will be calculated as the number of incident events per 100 person years, with exact-Poisson based confidence intervals.
 - c. On Study Product (OSP) HIV incidence. Events, and person time will be classified as in (b) above, however the OSP analysis will define CAB exposure to include only injections and only events and person time that occur within 10 weeks of the last non-delayed injection (or within 6 weeks of the last injection if only one injected was given).

2. Evaluate the safety of CAB during unblinded follow-up, and in the OLE. Compare with the blinded period.

For CAB-LA safety, participants are excluded from the cohort if they never receive any CAB. Safety evaluation ends one year after the last injection. The blinded period will end on the first visit before May 14, 2020; the unblinded period will begin the day after the blinded period ends until the first OLE visit for each participant, and the OLE period will extend from the first OLE visit until the last study visit.

- a. Oral CAB step. For the blinded and OLE stages: Counts and proportions of participants reporting any Grade 2+ AEs occurring after the receipt of oral CAB, up to 2 weeks following the last planned oral dose, and prior to the first injection. Events will be tabulated by blinded and OLE stages, overall and by grade.**
 - b. Overall CAB safety. Counts and proportions of participants reporting any Grade 2+ AEs after receiving at least one dose of oral or injectable CAB, with onset date up to one year following the last injection. For blinded stage, all events up through May 14, 2020, are tabulated; for unblinded, all events up through the participant OLE visit; for OLE all events with onset date up to one year following the last injections. Events will be tabulated by blinded, unblinded and OLE, overall and by grade.**
 - c. Evaluating the OLI. Among participants assigned to the TDF/FTC arm who elect to initiate CAB, counts and proportions of participants reporting one or more Grade 2+ AEs or any event leading to product discontinuation within the first 12 weeks and within the first 48 weeks of initiating CAB injections comparing participants who received an oral lead in (OLI) to those who chose direct to inject. Events will be tabulated overall and by grade; for events of interest, rates of events may be computed to enable statistical comparison. ISRs will not be considered in the evaluation in this comparison.**
 - d. Injection site reactions. Counts and proportions of ISRs reported by all participants will be tabulated by blinded, unblinded and OLE amongst those receiving at least one CAB injection, overall, by injection number, and by severity.**
- 3. Estimate HIV incidence in participants who choose to receive TDF/FTC during the OLE, separately and in combination with incidence amongst those assigned to TDF/FTC during the unblinded period. Compare with HIV incidence in those assigned to TDF/FTC during the blinded period.**
- a. As per section (1) above the timing of incident infections will be calculated based on the first-positive date determined by the EAC, and person time will be classified on an individual basis depending on OLE entry dates. In blinded and unblinded follow-up, all person time from participants assigned to TDF/FTC will be included. In OLE follow-up, Step 3 events (i.e., events occurring after a decision to stop CAB-LA injections and initiate TDF/FTC) will not be included. However, for participants initially assigned to CAB-LA who switch to TDF/FTC, and participants assigned to TDF/FTC who choose to continue TDF/FTC during the OLE, all events and person time will be included starting with the date TDF/FTC is initiated/continued in the OLE. Incidence rates and confidence intervals will be computed as above.**

4. Evaluate safety and HIV incidence among participants who receive TDF/FTC dosing during temporary discontinuation (e.g. due to lack of access during COVID) of CAB injections.
 - a. For participants who were assigned to CAB (oral or injectable) and temporarily switched to TDF/FTC, then return to CAB, tabulate the number and proportion who report grade 2 or higher AEs within 12 weeks (first two injection cycles) of the first post-TDF/FTC dose of CAB.
 - b. HIV incidence rates will be calculated during and following the CAB-discontinuation period, where the discontinuation period begins at the time of TDF/FTC initiation, and ends at the first post-discontinuation CAB dose.
5. Summarize PrEP choice at entry into OLE, including the number/proportion of participants who elect to (a) CAB-arm: continue on CAB, (b) CAB-arm: switch from CAB to TDF/FTC at entry into OLE, (c) CAB-arm: switch back from TDF/FTC to CAB at entry into OLE, (d) CAB-arm: stay on TDF/FTC, (e) TDF /FTC-arm: switch to CAB, and (f) TDF/FTC-arm: remain on TDF/FTC. And, among those initially assigned to TDF/FTC who choose to initiate CAB during the OLE, how many elect oral lead in and how many elect direct to inject.
 - a. Counts and proportions will be presented in tabular form by arm
6. Assess CAB continuation and adherence (i.e. acceptability) during the OLE and unblinded stage compared to the blinded period.
 - a. Time from initiation of CAB injections to discontinuation, defined as not receiving an injection within 16 weeks of the prior injection, will be plotted using the product limit method, separately by period/arm (blinded, unblinded, and TDF/FTC-arm participants choosing CAB during the OLE), and aggregated across all periods.
 - b. Proportion of injections that were given more than 8, 10, and 12 weeks from the prior injection compared between the blinded, unblinded, and OLE (participants choosing CAB-LA in both arms), (noting that potential COVID-related delays may need to be accounted for). Analyses may be tabulated by injection number.
7. Assess tail-phase HIV incidence rates amongst those who discontinue CAB-LA injections.
 - a. A “tail-phase” infection is defined as an event that occurred in a participant who has received an CAB-LA injection and whose first HIV positive visit (per completion of extended central laboratory testing) occurred between 9 and 56 weeks of the last CAB LA injection.
 - b. Tail-phase person time will start from the first HIV-negative visit at approximately 8 weeks after the last CAB LA injection and end at the last visit (with HIV testing) within 56 weeks of the last injection. For participants who re-start CAB in the OLE prior to 56 weeks from their last injection, person time will be truncated at the date of their first CAB dose in the OLE.
 - c. Tail phase events from blinded, unblinded, and OLE follow-up time will all be included, with incidence rates and confidence intervals computed as described in section (1) above.

- 8. Genotypic resistance, drug concentrations, infection timing, and HIV testing results for all incident infections. Phenotypic INSTI resistance may also be evaluated in selected cases.**
 - a. Details of each confirmed incident HIV infection will be presented, including longitudinal CAB concentrations (tabular and plot), resistance mutations detected (tabular, by visit), and results of HIV testing performed at each visit (table).**
- 9. Evaluate weight changes over time among participants who transition from TDF/FTC to CAB during the OLE, and among participants who transition from CAB to TDF/FTC.**
 - a. Mean and median weight and BMI will be tabulated and plotted for the 12 months prior to the treatment transition point (TDF/FTC to CAB or CAB to TDF/FTC), and for 12 months after the treatment transition point. Changes over time will be computed and compared before and after the treatment transition using longitudinal random effects regression models with a term for time (years) and an interaction with an indicator for the post-transition time period.**
 - b. Paired weight changes over a fixed time period (e.g. 4 months) will be assessed in the cohort of participants who**
 - i. Were initially assigned to TDF/FTC and subsequently chose to initiate CAB-LA**
 - ii. Were initially assigned to CAB-LA, or chose CAB during the OLE, and subsequently switched to TDF/FTC.**

Each person in each of i) and ii) will contribute two weight changes (one when receiving each of the drugs). Weight changes for each person will be compared across the two drugs.
- 10. STI incidence rates to corroborate/contextualize HIV incidence rates as a biomarker of risk behavior**
 - a. Counts and incidence rates will be presented in tabular form for incident syphilis, gonorrhea (rectal and urethral), and chlamydia (rectal and urethral) for both the unblinded stage and the OLE period, separately and combined, using the same person time definitions for these time periods as described section (1) above. Repeat events within the same participant will be counted separately in the incidence calculations. Counts and rates will be presented by randomized arm for the blinded and unblinded stages, and by treatment choice for the OLE.**
- 11. Summarize reasons for choice/preferences for study product.**
 - a. A tabular summary of choices and preferences will be presented by arm for participants agreeing to participate in the OLE, and during the unblinded stage for participants who elected to stop randomized treatment at that time.**

7. Appendix V, Part C, Section 6, Procedures for Steps 4 and 5 (originally Steps 1 – 3 from Section 5.0, with modifications)

Reference to new [Table 11](#) is added for participants who receive the new study information but do not continue follow up under Version 4.0:

Procedures and evaluations for Steps 4 and 5 are outlined in Tables 7 – 10 and are not repeated here. **Table 11 details final procedures and evaluations for participants who receive the new study information but do not continue follow up under Version 4.0 because they do not want to or are ineligible to do so.** The HIV testing algorithm for follow-up visits is shown in Figure 10.

8. Appendix V, Part C, Section 8, Procedures for Participants Who Do Not Complete Step 4a (originally Step 1 from Section 5.12 of the main protocol, with modifications)

The original Table 11 is renumbered to Table 12. Only the impacted portion of this section is depicted:

Participants with HIV infection will be asked to be followed per Table ~~11~~**12** below.

9. Appendix V, Part C, Section 9, Procedures for Suspected or Confirmed HIV Infection (from Section 5.14.2 of the main protocol, with modifications)

Clarification for follow-up of participants who have a reactive or positive HIV test during Version 4.0 is added. Only the impacted portion of this section is depicted:

Note: Participants who became infected with HIV under Version 3.0 of the protocol and are being followed on the HIV infection quarterly visit schedule will complete their visits under this Version 4.0 amendment. For example, if they completed Weeks 0, 12, and 24 under Version 3.0 and Version 4.0 is now approved at the site, the participant will complete Weeks 36 and 48 under Version 4.0 and be terminated from the study. **Participants who are found to have a positive or reactive HIV test during consent to or participation in Version 4.0 and have ever received an active CAB injection at any time during previous study conduct will be followed according to Table 12 - Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result. Participants who have a positive or reactive HIV test during Version 4.0 and have received only oral TDF/FTC and/or oral CAB but never an active CAB injection at any time during previous study conduct will be referred to local care for ART if HIV infection is confirmed based on testing performed at study sites; there will be no further study follow-up for these participants once HIV infection is confirmed.**

10. Appendix V, Part C, Section 10, Sexually Transmitted Infections (from Section 5.15 of the main protocol)

Further guidance is added regarding the timing of STI testing upon entry to Version 4.0. Only the new text of this section is depicted:

Upon entry into Version 4.0, any participant who has not had asymptomatic STI screening in the previous 6 months should have STI testing performed at that Version 4.0 initial visit.

11. Appendix V, Part D, Schedules of Procedures and Evaluations for Steps 4 a-c and 5, and for Participants who are Not Continuing under Version 4.0

Text is updated to include participants who receive the new study information but do not continue follow up under Version 4.0.

See Tables 7 – ~~1011~~ for corresponding Schedules of Procedures and Evaluations for Steps 4 a-c, **and Step 5, and participants not continuing under Version 4.0**, as well as Table ~~1112~~ for participants who become infected with HIV during the time of this amendment. Refer to the Schedule of Forms (in SSP Section VIII) as well as instructions on the forms for whom and when to administer forms.

12. Appendix V, Part D, Tables 7-12: Schedules of Procedures and Evaluations

Asymptomatic STI screening is added at Day 0 of each step only if this testing was not performed in the previous six months on study. Footnotes are updated to reflect the STI testing schedule as well as to clarify assessment of injection site reactions. Table 8 is updated to allow 120 days between Step 4a Day 0 and Step 4b Day 0 to accommodate 50% adherence to oral CAB in Step 4a. Table 11 is a new table for participants who are not continuing study under Version 4.0. The note for Table 12 is updated to clarify that participants who are not continuing under Version 4.0 will be referred to local care if found to have HIV infection at their final visit. Only the impacted sections from these tables are depicted:

a. Table 7: STEP 4a Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL for participants initiating CAB injections

Procedures	DAY 0	WEEK 4
Urine collection for GC/CT testing ⁵	X	
Rectal swab collection for GC/CT testing ^{5, 6}	X	
Syphilis serologic testing ⁵	X	
Urine GC/CT testing ⁵	X	
Rectal swab GC/CT testing ⁵	X	

FOOTNOTES FOR TABLE 7:

⁵ Perform testing at Day 0 only if not done within the last 6 months

⁶ If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

b. **Table 8: STEP 4b Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – for participants initiating or restarting CAB injections**

Procedures*	DAY 0
Urine collection for GC/CT testing ⁷	X
Rectal swab collection for GC/CT testing ^{7, 8}	X
ISR evaluation ⁹	X
Syphilis serologic testing ⁷	X
Urine GC/CT testing ⁷	X
Rectal swab GC/CT testing ⁷	X

FOOTNOTES FOR TABLE 8:

*Participants who opted into Step 4a must complete Step 4b Day 0 and receive their first injection within **8 weeks 120 days** of starting Day 0 of Step 4a.

⁷ Perform testing at Day 0 only if not done within the last 6 months

⁸ If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

⁹ An ISR typically begins 24-48 hours after an injection. The “X” marked in this Day 0 box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at this visit at any point later that day and onward (as reported by the participant). A participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not actively solicit this information from participants, either in-person or remotely. Should ISR symptoms be reported by the participant, it should be reported as an ISR for the injection that occurred at this visit. If an ISR is reported, use the Injection Site Reaction eCRF. As a reminder, symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.

c. **Table 9: Step 4c Schedule of Procedures and Evaluations – Cabotegravir Injections**

Procedures*	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Urine collection for GC/CT testing ⁹	X			X			X
Rectal swab collection for GC/CT testing ^{2, 9}	X			X			X
ISR evaluation ¹⁰	X	X	X	X	X	X	X
Syphilis serologic testing ⁹	X			X			X
Urine GC/CT testing ⁹	X			X			X
Rectal swab GC/CT testing ⁹	X			X			X

FOOTNOTES FOR TABLE 9:

² If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

⁹ Perform testing at Day 0 only if not done within the last 6 months; perform testing at all other visits as noted

¹⁰ An ISR typically begins 24-48 hours after an injection. The “X” marked in each visit box pertains to reporting an ISR if a participant experiences signs and symptoms of one (e.g., pain, redness, swelling, etc.) as a result of the injection that occurred at that visit at any point later that day and onward (as reported by the participant). A participant may follow-up with the site before their next visit to report that they have experienced an ISR or they may report it at their next visit. Sites need not actively solicit this information from participants, either in-person or remotely. Should ISR symptoms be reported by the participant, it should be reported as an ISR for the visit at which that injection occurred. If an ISR is reported, use the Injection Site Reaction eCRF. As a reminder, symptoms experienced immediately at the time of an injection are NOT considered ISRs. No ISR assessment is required at the visit at which the injection is provided.

d. **Table 1: STEP 5 Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC**

Procedures*	Day 0	*Weeks 12, 36 (60, 84, 108, 132, if required)	*Week 24, 48 (72, 96, 120, 144, if required)
Informed consent/ "Choice" discussion ⁹	X		
Urine collection for GC/CT testing and urinalysis ¹	X		X
Rectal swab collection for GC/CT testing ^{1, 2}	X		X
Syphilis serologic testing ¹	X		X
Urine GC/CT testing ¹	X		X
Rectal swab GC/CT testing ¹	X		X

FOOTNOTES FOR TABLE 10:

¹ Perform testing at Day 0 only if not done within the last 6 months prior to Day 0; perform testing at all other visits as noted may be deferred at the discretion of the site investigator.

⁹ This procedure is required only if the participant did not complete Step 4.

e. **Table 11: Schedule of Procedures and Evaluations – For Participants Who Are Not Continuing Under Version 4.0**

Procedures	DAY 0
Informed consent/ New information discussion	X
Locator Information	X
HIV counseling	X
Offer condoms and lubricant	X
Blood collection	X
Urine collection for GC/CT testing ¹	X
Rectal swab collection for GC/CT testing ^{1, 2}	X
HIV testing ³	X
Syphilis serologic testing ¹	X
Urine GC/CT testing ¹	X
Rectal swab GC/CT testing ¹	X
Plasma storage	X
DBS storage	X

¹ Perform testing at Day 0 only if not done within the last 6 months

² If testing cannot be performed at the local laboratory, testing at another laboratory will be considered (see SSP Manual).

³ The HIV testing algorithm is provided in Figure 10 below and Appendix VIII of the SSP Manual. If HIV rapid testing is indicated, this testing may be performed in the clinic or the laboratory.

f. **Table 12: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)**

Only the note is impacted and depicted below:

Note 1: The procedures listed for the HIV Confirmation Visit apply to participants who ~~become infected~~ **have a reactive or positive HIV test** during Steps 4 a-c and 5, **or at their final study visit if not continuing participation under Version 4.0. Participants who have a positive or reactive HIV test during Version 4.0 or at their final study visit (if not continuing under Version 4.0) and have ever received an active CAB injection at any time during previous study conduct, will be followed according to Table 12. Participants who have a positive or reactive HIV test during Version 4.0 or at their final study visit (if not continuing under Version 4.0) and have only ever received oral TDF/FTC and/or oral CAB but never an active CAB injection will be referred to local care.** The procedures listed for Weeks 12, 24, 36, and 48 apply only to participants with confirmed HIV infection during Steps 4b and 4c of the study. Participants with confirmed HIV infection in Step 5 of the study may undergo similar procedures as listed in Weeks 12, 24, 36, and 48, and will be determined by the members of 083CMC@hptn.org. Participants with confirmed HIV infection in Step 4a will be terminated from the study and referred to local care.

13. Appendix V, Part F, Addendum to the Main Sample Informed Consent Form

Asymptomatic STI screening is included at Day 0 of each step only if this testing was not performed in the previous six months on study. Footnotes are added to reflect the STI testing schedule. A new table is added for the final visit of participants who receive the new study information but do not continue follow up under Version 4.0. Text is added to clarify which final visit procedures will be conducted depending on participation in Version 4.0. Text is updated to clarify follow up for participants found to have HIV infection during Step 5 depending on whether they have ever received a CAB injection. The signature page is updated to reflect the options for final visit procedures for participants who receive the new study information but do not continue follow up under Version 4.0. Only the impacted parts of this section are depicted:

a. STEP 4a: Schedule of Procedures and Evaluations – Daily Oral Cabotegravir – OPTIONAL if you choose to start CAB for the first time

Procedures	DAY 0	WEEK 4
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, to check your general health, the health of your liver and kidneys, and for storage	X	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X	

* If you have had syphilis, gonorrhea, and chlamydia testing within 6 months of joining this part of the study, this testing will not be done at Day 0 unless you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

b. STEP 4b: Schedule of Procedures and Evaluations – Loading Dose Cabotegravir Injection – If you are initiating or restarting CAB injections

Procedures	DAY 0
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, to check your general health, the health of your liver and kidneys, and for storage	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X

* If you have had syphilis, gonorrhea, and chlamydia testing within 6 months of joining this part of the study, this testing will not be done at Day 0 unless you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

c. STEP 4c: Schedule of Procedures and Evaluations – Cabotegravir Injections - if you choose to continue CAB injections

Procedures	DAY 0	WEEK 8	WEEK 16	WEEK 24	WEEK 32	WEEK 40	WEEK 48
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); to check your general health and the health of your liver and kidneys (Week 0, 24 and 48 only); for storage (every visit); HCV testing (Week 48 only); and Syphilis testing (Day 0*, Weeks 24 and 48 only)	X	X	X	X	X	X	X
Perform a swab of your rectum and collect urine to test for gonorrhea and chlamydia*	X			X			X

* If you have had syphilis, gonorrhea, and chlamydia testing within 6 months of joining this part of the study, this testing will not be done at Day 0 unless you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

d. STEP 5: Schedule of Procedures and Evaluations – Open Label Daily Oral TDF/FTC - If you choose to stay on or switch to TDF/FTC, or after you complete Step 4c

Procedures	Day 0	Weeks 12, 36 (60, 84, 108, 132, if required)	Week 24, 48 (72, 96, 120, 144, if required)
Collect ~XX mL (about x teaspoons) of blood for HIV testing (every visit); syphilis testing (Day 0*, then every 6 months only); to check your general health and the health of your liver and kidneys (Day 0, then every 6 months only); the amount of the study drug in your blood, and for storage (every visit)	X	X	X
Perform a swab of your rectum; collect urine for urinalysis and gonorrhea and chlamydia testing*	X		X

* If you have had syphilis, gonorrhea, and chlamydia testing within 6 months of joining this part of the study, this testing will not be done at Day 0 unless you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

- e. **Not continuing in this part of the study: Schedule of Procedures and Evaluations – If you decide you do not want to participate in this part of the study, or you have reached 3 years from your enrollment date and do not want to start CAB, or you are otherwise not eligible to participate in this part of the study, we will ask you to do these procedures as your final visit:**

Procedures	Day 0
Confirm where you live and how to contact you	X
Talk with you about HIV and ways to protect yourself from getting it	X
Offer you condoms and lubricant	X
Collect ~XX mL (about x teaspoons) of blood for HIV testing, syphilis testing*, and storage	X
Perform a swab of your rectum and collect urine for gonorrhea and chlamydia testing*	X

* If you have had syphilis, gonorrhea, and chlamydia testing within 6 months of this part of the study, this testing will not be done at Day 0 unless you have symptoms or report a recent exposure to someone with one of these sexually transmitted infections

f. IF YOU LEAVE THE STUDY BEFORE YOUR FINAL VISIT:

If you **join this part of the study and then** leave the study before **your finalthe last** visit **of the study schedule**, we will ask you to complete a final study visit if you are available to do so. The final study visit will include the requirements for the visit at which it is confirmed you are leaving the study, and you will not receive CAB or TDF/FTC study product at this visit. Also, if you are on TDF/FTC and leave the study prior to your final visit, we will ask you to return any unused study product.

g. If you become infected with HIV during this part of the study

If you get HIV during Step 4a, you will stop taking the CAB pills, and you will be referred for local care and treatment of HIV and will be discontinued from the study. If you get HIV during Step 4b or 4c (while you are getting shots), you will stop getting any further shots and we will ask you to come back for a visit every 3 months for about a year. If you get HIV during Step 5 of the study, you will stop taking the TDF/FTC pills and will be referred for local care and treatment of HIV, **and. If you are found to have HIV at your final study visit or during Step 5 and you have ever had a CAB injection at any time during past study visits**, we will ask you to come back for a visit every 3 months for about a year; **if you did not receive any CAB injections during past study visits, you will be discontinued from the study.**

h. Signature Page

See next page

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 4.0

February 10, 2021

[Insert signature blocks as required by the local IRB:] If you have read this addendum to the main consent form, or had it read and explained to you, and you understand the information, **and you voluntarily agree to continue in this part of the study,** please **initial the one line that applies to you based on if you want to continue in the study, you no longer want to continue in the study, or you are not eligible to continue in the study. Then** sign your name or make your mark below.

_____ I **voluntarily** agree to **take part-continue** to take part in this **part-portion** of the study.

_____ I **do not agree** to take part in this **part-portion** of the study, **but I do agree to the procedures listed in the table for not continuing in this part of the study.**

_____ **I do not agree** to take part in this portion of the study, and **I do not agree to the procedures listed in the table for not continuing in this part of the study.**

_____ **I understand I am not eligible** to take part in this portion of the study, and **I do agree to the procedures listed in the table for not continuing in this part of the study.**

_____ **I understand I am not eligible** to take part in this portion of the study, and **I do not agree to the procedures listed in the table for not continuing in this part of the study.**

Participant Name (print)

Participant Signature and Date

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

Witness Name (print)
(As appropriate)

Witness Signature and Date