

**Letter of Amendment # 4 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 1.0, February 2, 2016**

**DAIDS Document ID: 20725**

**IND # 122, 744**

**Final Version of LoA # 4: 14 December 2017**

The information contained in this Letter of Amendment (LoA) impacts the HPTN 083 study, including the study informed consent forms, and 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. Note that all required approvals of protocol Version 1.0, LoA # 1, LoA # 2, LoA # 3 and LoA # 4 must be obtained before initiating this study for sites that have not initiated the study at the time LoA # 4 was distributed to the sites.

Upon receiving IRB/EC approval, and approval of any other applicable regulatory entities, study sites must submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). 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, 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.

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## Summary of Revisions and Rationale

**Revision 1:** Four new appendices are added to the protocol; these are added to the Table of Contents.

**Revision 2:** The protocol team roster is updated to include current contact information for Sheldon Fields and Steve Safren. The roster is also updated to add Katherine Shin, who is the current Division of AIDS (DAIDS) protocol pharmacist on the study, and who replaces Bijal Patel, the previous DAIDS protocol pharmacist, who has left DAIDS. As such, Bijal Patel is removed from the roster (she was added in LoA # 2, dated July 26, 2016). Philip Sullivan is also added to the protocol roster, who has joined the team from the HPTN Laboratory Center as a QA/QC coordinator.

**Revision 3:** A Protocol Signature Page is added per new DAIDS policy.

**Revision 4:** An error is fixed in the Schema to cite the correct email alias for members of the HIV endpoint committee.

**Revision 5:** The bone mineral density subset was erroneously referred to as a sub study in Section 1.8, which has been fixed. It also erroneously stated that participation in the subset would be stratified across regions, which is not the case. Additionally, language is added to state that the substudy will be competitively enrolled until the total of 350 is reached.

**Revision 6:** An error is fixed in Section 2.5 to cite the correct email alias for members of the HIV endpoint committee.

### **Revision 7 a-b:**

- a. Minor updates are made to the descriptions of the study drugs in both arms for clarity in Section 4.1
- b. Language is added and modified in Section 4.2.3 to state that vials of cabotegravir may come in 2mL or 3mL vials, and to capitalize “Celcius.”

### **Revision 8 a - f:**

- a. Language is added and modified to the first paragraph under Section 5.0 to reference four new appendices added to the protocol. Appendix Id is the schedule of procedures and evaluations for annual HIV testing visits, and appendices I e – g are the HIV testing algorithms required at screening, enrollment and follow-up, respectively.
- b. Language is added to Section 5.3 to clarify that participants who do not transition from Step 1 to Step 2 will be followed annually for HIV testing until all participants complete Step 2 of the study. This change is made in order to be consistent with the principles of an Intent-to-Treat (ITT) analysis, with all randomized participants intended to be followed on blinded study products for the same amount of time. Additionally, the procedures for the annual HIV testing visits are included.
- c. Language is added and modified to state that windows for protocol-specified visits are contiguous, and referred to as target and allowable windows. Therefore, there are never out of window visits. The title of the section is also updated since the text refers to any protocol-specified visit, not just injection visits.
- d. Language is added and modified in Section 5.11 regarding participants who do not transition to the injection phase of the study or who do not complete the full course of injections. These participants will be followed annually for HIV testing until all participants complete in Step 2 of the study (as per above regarding ITT analysis); again, participants who do not complete the full course of injections will complete Step 3 of the study and THEN begin annual follow-up for HIV testing until all participants

complete Step 2 of the study. Much of this language was modified in Letter of Amendment # 3, dated November 10, 2016; however, further modifications have been made for clarity. Additionally, the procedures for the annual HIV testing visits are included.

e. Language is added and modified in Section 5.13.1 regarding “split” enrollment visits for clinical sites that have pharmacies located off-site.

f. An error is fixed in Section 5.13.2 to cite the correct email alias for members of the HIV endpoint committee.

**Revision 9 a – c:**

a. Section 6.3 is modified to state that Grade 1 and higher clinical adverse events as well as Grade 2 and higher laboratory adverse events will be reported into the study database. Additionally, the current DAIDS Table for Grading Adult and Pediatric Adverse Events is updated; language is deleted stating that this version will be used for the entire duration of the study in case another version becomes available during the course of the study and determined necessary to be used in the study.

b. Language is modified in Section 6.4.2 regarding the reporting of Grade 1 and higher adverse events to be included in reports to the FDA and other regulatory authorities as applicable.

c. Language is modified in Section 6.4.3 regarding the current DAIDS Table for Grading Adult and Pediatric Events.

**Revision 10:** Per DAIDS policy, language is added and modified in Section 8.4 – Confidentiality to state that other regulatory entities (in addition to the previously specified US FDA) may review study records. This is important at the time of non-US FDA regulatory audits. See also Revision 15d below.

**Revision 11:** Per Section 5.11 (see Revision 8c above), a new appendix is added for the procedures and evaluations for annual HIV testing participants in Step 1 that do not transition to Step 2 or for participants in Step 2 that prematurely stop getting injections.

**Revision 12 a – c:** Three appendices are added to the protocol which depict the algorithm for HIV testing at screening, enrollment and follow-up during all protocol-specified visits. These algorithms have been included in the accompanying study specific procedures (SSP) manual since the inception of the study protocol, as well as in all training materials; however, due to recent errors at some of the sites regarding adherence to these algorithms, the team decided it was also important to include them in the protocol document.

**Revision 13:** A note is added to Appendix II referencing procedures in the SSP for discordant or discrepant HIV test results.

**Revision 14 a – c:**

a. Language is added under the “Toxicity Management General Guidance” section of Appendix III to contact the Clinical Management Committee for Grade 3 abnormalities identified at study enrollment.

b. Language is modified in Appendix III to state that participants that do not complete the full course of injections will be following annually for HIV testing until all participants complete Step 2 of the study.

c. Language is modified for toxicity management of creatinine phosphokinase (CK or CPK) as outlined in Appendix III.

**Revision 15 a – d – Revisions to the Sample Screening and Enrollment Informed Consent Form:**

- a.** Language is added to state that there may be circumstances where unforeseen or unanticipated events occur leading to interim visits that may require additional procedures and sample collection.
- b.** Per revisions outlined above, language is added regarding the procedures for annual HIV testing in the event that a participant in Step 1 does not transition to Step 2 or a participant in Step 2 stops getting injections prematurely.
- c.** Additional side effects are added for cabotegravir in order to harmonize across other on-going cabotegravir studies being conducted and sponsored by ViiV Healthcare, the pharmaceutical manufacturer of cabotegravir. To be clear, these changes were not prompted by specific events in the the HPTN 083 study.
- d.** Per DAIDS policy, language is added to state that other regulatory entities (in addition to the previously specified US FDA) may review study records. This is important at the time of non-US FDA regulatory audits.

## IMPLEMENTATION

### **Revision 1** Table of Contents

Note: Four appendices have been added to the protocol, including to the Appendices listed in the Table of Contents.

**APPENDIX ID: SCHEDULE OF PROCEDURES AND EVALUATIONS - ANNUAL HIV TESTING VISITS**

**APPENDIX IE: HIV TESTING ALGORITHM AT THE SCREENING VISIT**

**APPENDIX IF: HIV TESTING ALGORITHM AT THE ENROLLMENT VISIT**

**APPENDIX IG: HIV TESTING ALGORITHM AT FOLLOW UP VISIT**

### **Revision 2** Protocol Team Roster

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**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 1.0**

**February 2, 2016**

**Letter of Amendment # 4, 14 December 2017**

**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 4** SCHEMA

### **Step 3:**

Note: Only the second paragraph (out of two) of this section is impacted and included below.

A participant with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the members of the **Clinical Management Committee (CMC) [083HIV@hptn.org](mailto:083HIV@hptn.org) group.**

## **Revision 5** Section 1.8: Rationale for Bone Mineral Density Subset

Note: Only the second paragraph (out of two) of this section is impacted and is included below.

At sites that have the ability to perform DXA scans, 175 participants in each arm (350 participants in total) will be offered participation in a DXA **subset study**. DXA evaluations will be conducted for **subset study** participants at Enrollment and Weeks 57 and 105. An additional informed consent will be required for **subset sub-study** participation, **and participation will be stratified across regions to provide broad geographic and racial/ethnic representation in the sub-study. The subset will be competitively enrolled until 350 baseline DXA scans are obtained.**

## **Revision 6** Section 2.5: Study Design and Overview

Note: Only the second paragraph under Step 3 of this section is impacted and is included below.

### **Step 3:**

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the **CMC [083HIV@hptn.org](mailto:083HIV@hptn.org) group.**

## **Revisions 7 a - b** REVISIONS TO STUDY PRODUCT CONSIDERATIONS SECTION

### **7a. Section 4.1: Study Product Regimens/Administration/Formulation Content**

#### Study Product Regimens

Step 1 - Participants will be randomized 1:1 to one of two study arms:

- Arm A: Oral CAB tablets 30 mg, **one tablet orally daily for five weeks, with or without food and AND** placebo for TDF/FTC tablet, **two one** tablets **orally** daily for 5 weeks, with or without food
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination tablets, **one tablet orally daily for five weeks, with or without food and AND** placebo for oral CAB tablets, **orally two tablets** daily for 5 weeks, with or without food



Step 2 – Blinded injections and blinded daily oral pills:

- Arm A: CAB LA 600 mg administered as one 3 mL (600 mg) **intramuscular** (IM) injection in the gluteal muscle at two time points 4 weeks apart and every 8 weeks thereafter, **and AND** placebo for TDF/FTC **daily-oral** tablet, **one tablet orally daily with or without food**
- Arm B: TDF/FTC 300 mg/200 mg fixed dose combination **daily-oral** tablets, **one tablet orally daily, with or without food and AND** placebo for CAB LA (**Intralipid 20% fat emulsion infusion**) administered as one 3mL **(600 mg) intramuscular (IM)** injection in the gluteal muscle as two time points 4 weeks apart and every 8 weeks thereafter

Step 3: ~~For a~~**All** participants **transitioned to this step**, including those who permanently discontinue receiving injections before their Step 2 participation in the study ends, **will receive** open-label TDF/FTC 300 mg/200 mg fixed dose combination **daily-oral** tablets, one tablet **orally** daily for up to 48 weeks.

#### 7b. Section 4.2.2: Injectable Suspension

Note: Only the first paragraph of this section is impacted and is included below.

CAB LA is formulated as a sterile white to slightly colored suspension containing **400mg/2mL 200 mg/mL** of CAB LA for administration by intramuscular (IM). The product is packaged in a **3-mL vials 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 at 2 degrees **eCelsius** to 30 degrees **eCelsius** (2° C – 30° C), do not freeze.

### **Revision 8 a - f** REVISIONS TO STUDY PROCEDURES SECTION

#### 8a. Section 5.0 - STUDY PROCEDURES

Overviews of the study visit and procedures schedules are presented in Appendices I ~~a-e~~ **a - d**, and Appendix II in the event of suspected and confirmed HIV infection. **Appendices I e – g include the required HIV testing algorithm for screening, enrollment and follow-up, respectively (these are also included in the SSP)**. Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites are included in the SSP Manual.

#### 8b. Section 5.3: Step 1: Weeks 2 and 4 – Oral Safety Visits

Note: Only the “Notes for Weeks 2 and 4” portion of this section is impacted and included below.

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  $\leq$  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 for HIV testing **only until all participants complete Step 2 of the study**. 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.

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 for HIV testing **only until the all participants complete** Step 2 of the study. 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.

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 for HIV testing **only until the all participants complete conclusion of** Step 2 of the study. AEs will be followed until resolution ( $\leq$  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 for HIV testing **only until the all participants complete conclusion of** Step 2 of the study. All such cases must be reported to the CMC.

The CMC should be contacted for guidance regarding pill counts resulting in less than 75% adherence prior to the Week 5 First Injection Visit, or any other concerns regarding adherence.

**For participants who do not transition to Step 2 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**
- **HIV testing, plasma storage, DBS storage**
- **Offer condoms and lubricant**

#### **8c. Section 5.9: Injection Visit Windows**

The 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. **If a participant is unable to report to the visit during this time frame, or if the participant misses their appointment within this time frame, the CMC must be contacted for consultation regarding whether rescheduling outside of the visit window is allowable. —Broader,**

allowable visit windows are also defined in the SSP Manual 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; however, for injection visits, the CMC must be consulted in advance regarding additional clinical considerations for the timing of injections.

#### 8d. Section 5.11: Procedures for Participants Who Do Not Complete the Full Course of Injections

Note: The revisions included in purple highlight below are included in Letter of Amendment (LoA) # 3, dated November 10, 2016. Changes and updates to some of the language in LoA # 3 are included in this LoA # 4, and noted in yellow highlight.

~~Participants on either arm who have received at least one injection and refuse further injections or discontinue due to an AE will enter Step 3 and be followed on open label TDF/FTC according to Step 3 Arm A assessments; such participants will remain blinded to their original randomized assignment.~~

Participants in Step 1 of the study who are unable to transition to Step 2 of the study receive the first injection for any reason other than HIV infection will be terminated from the study asked to attend annual follow-up visits for HIV testing followed on an annual basis until all participants complete Step 2 of the study. (refer to SSP Manual). These participants will remain blinded to their original randomized assignment until all participants Step 2 of the study. Participants with confirmed HIV infection during Step 1 of the study If the reason is due to HIV infection, those participants will not transition to Step 2 of the study, but will be referred to care and will be terminated from the study.

Participants in Step 2 of the study that prematurely no longer receive stop receiving injections due to any reason other than HIV infection will be asked to transition to Step 3 of the study. Once that participant has completed the required 48 weeks on Step 3, they will then be transitioned to local prevention services and asked to continue to attend annual follow-up visits for HIV testing 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.

Sites should contact [083HIV@hptn.org](mailto:083HIV@hptn.org) for guidance regarding study visit procedures for participants that become HIV-infected during Step 3 of the study.

~~Participants who are unable to receive the first injection for any reason will be terminated from the study. If the reason is due to HIV infection, those participants will be referred for care and will be terminated from the study.~~

For participants that transition to annual HIV testing 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

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

#### 8e. Section 5.13.1: Screening and Enrollment

Individuals who have one or more reactive or positive HIV tests at **the Screening or Enrollment visit** are not eligible to participate in this study. Furthermore, at the Screening and Enrollment **visit** (at Enrollment, prior to randomization; **and for sites that do split enrollment visits due to physical location constraints, prior to administration of study product**), individuals with any signs or symptoms consistent with acute (pre-seroconversion) HIV infection will not be enrolled, unless acute HIV infection is ruled out with appropriate laboratory testing, in consultation with the CMC. Signs and symptoms consistent with acute HIV infection will be included in the SSP Manual.

#### 8f. Section 5.13.2: Follow-up (after study Enrollment)

Note: Only the sixth paragraph of this section is impacted and included below.

Participants with confirmed HIV infection during Step 3 will be followed at least for the duration of Step 3, with possible additional assessments and follow-up to be determined by the **CMC083HIV@hptn.org group**.

### **Revisions 9 a - c** REVISIONS TO SAFETY MONITORING AND ADVERSE EVENT (AE) REPORTING SECTION

#### 9a. Section 6.3: Adverse Event Definition and Reporting

Note: Only the third paragraph of this section is impacted and included below.

Study site staff will document in source documents and the appropriate **e-CRF AEs (Grade 2 1 and higher clinical AEs, as well as Grade 2 and higher laboratory AEs, and any AE (clinical or laboratory) that leads to a study product hold (temporary or permanent) will be captured on AE e-CRFs) reported by or observed in enrolled (defined as after randomization has occurred) study participants regardless of severity and presumed relationship to study product. AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 2.0, November 2014 2.1 corrected, July 2017. This version will be used for the entire duration of the study.**

#### 9b. Section 6.4.2: Reporting Requirements for this Study

Note: Only the last paragraph in this section is impacted and included below.

Information on Grade **2 1** and higher AEs will be included in reports to the US FDA, and other government and regulatory authorities as applicable. Site staff will report information regarding AEs to their IRB in accordance with all applicable regulations and local IRB requirements.

#### 9c. Section 6.4.3: Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, **Corrected Version 2.0, November 2014 2.1, July 2017**, will be used for ~~the entire duration of the study for~~

determining and reporting the severity of adverse events. The DAIDS grading table is available on the DAIDS RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

**Revision 10** REVISIONS TO HUMAN SUBJECTS CONSIDERATIONS SECTION

8.4 Confidentiality

Note: Only the second paragraph in this section is impacted and depicted below.

Participant’s study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; pharmaceutical sponsors; representatives of the HPTN LOC, SDMC, and/or LC; the US FDA, OHRP, ~~other government and regulatory authorities~~, **other U.S., local and international regulatory entities**, and/or site IRBs.

**Revision 11** Appendix ID: Schedule of Procedures and Evaluations for Annual HIV Testing Visits

Note: This is a new Appendix added to the protocol.

**Appendix ID: Schedule of Procedures and Evaluations for Annual HIV Testing Visits**

**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 HIV testing visits until all participants complete Step 2 of the study.**
- **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 HIV testing visits until all participants complete Step 2 of the study.**

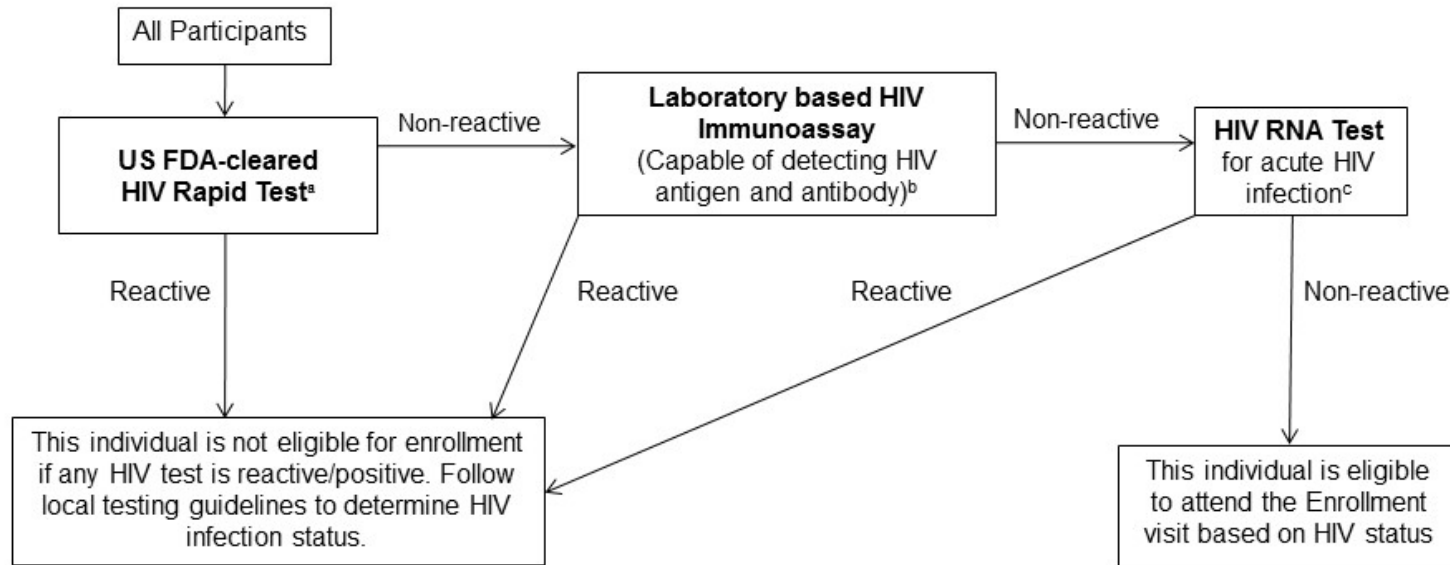
**In both cases above , these participants will remain blinded to their original randomized assignment until all participants complete Step 2 of the study.**

<b>Procedure</b>	<b>Annual HIV Testing Visit</b>
<b>Locator information</b>	<b>X</b>
<b>Offer condoms and lubricant</b>	<b>X</b>
<b>HIV counseling (pre- and post-test)</b>	<b>X</b>
<b>Targeted history, con meds, physical exam</b>	<b>X</b>
<b>Blood collection</b>	<b>X</b>
<b>HIV testing</b>	<b>X</b>
<b>Plasma storage</b>	<b>X</b>
<b>DBS storage</b>	<b>X</b>

**Revision 12a – c:** REVISIONS TO ADD THREE NEW APPENDICES FOR HIV TESTING ALGORITHMS

Revision 12a: Appendix IE: HIV Testing Algorithm at the Screening Visit:

**HIV Testing Algorithm at Screening\***



**NOTES:**

\* Site-specific HIV testing plans must be approved by the HPTN LC before the study opens.

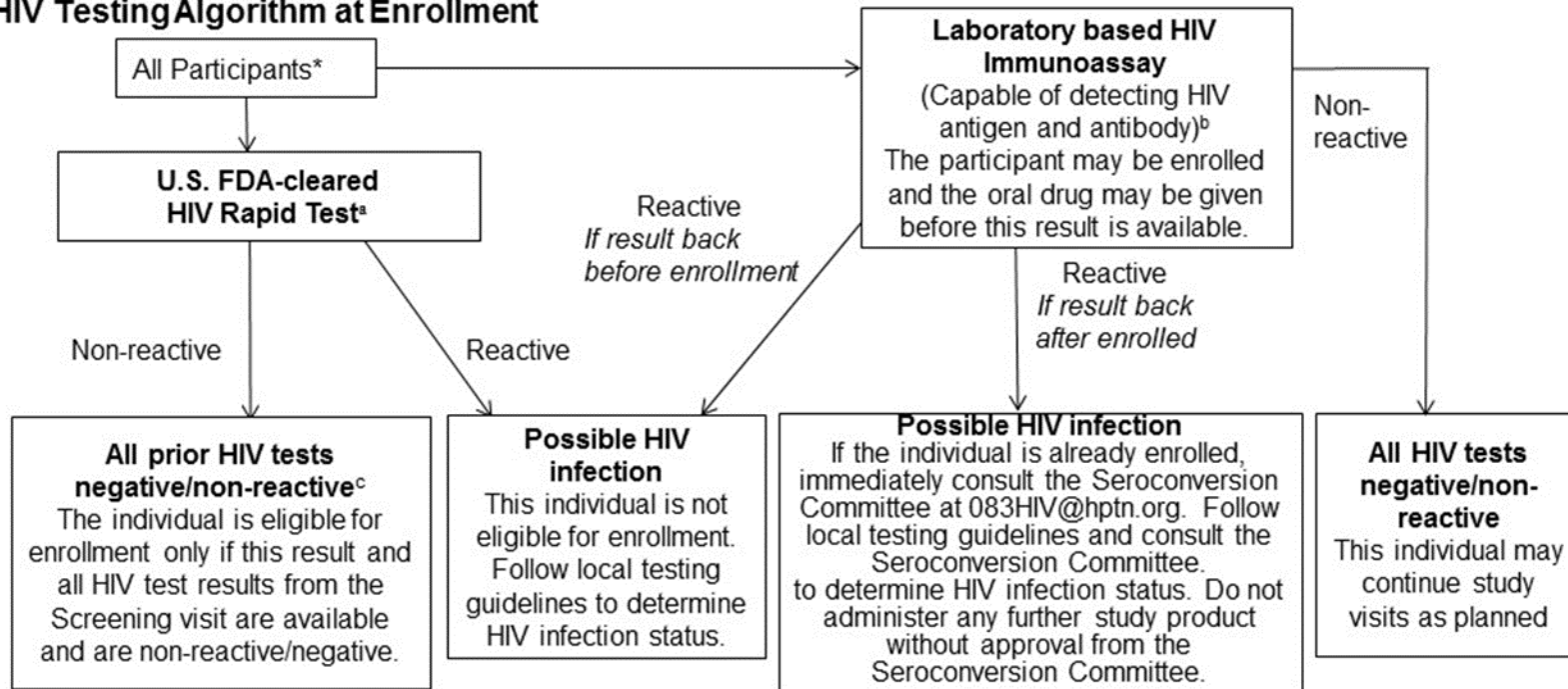
<sup>a</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>b</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> Screening for acute infection should be performed using an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for this testing, such as the APTIMA HIV-1 RNA Qualitative Assay. RNA test results must be obtained from a specimen collected within 14 days prior to enrollment.



### HIV Testing Algorithm at Enrollment



**NOTES:**

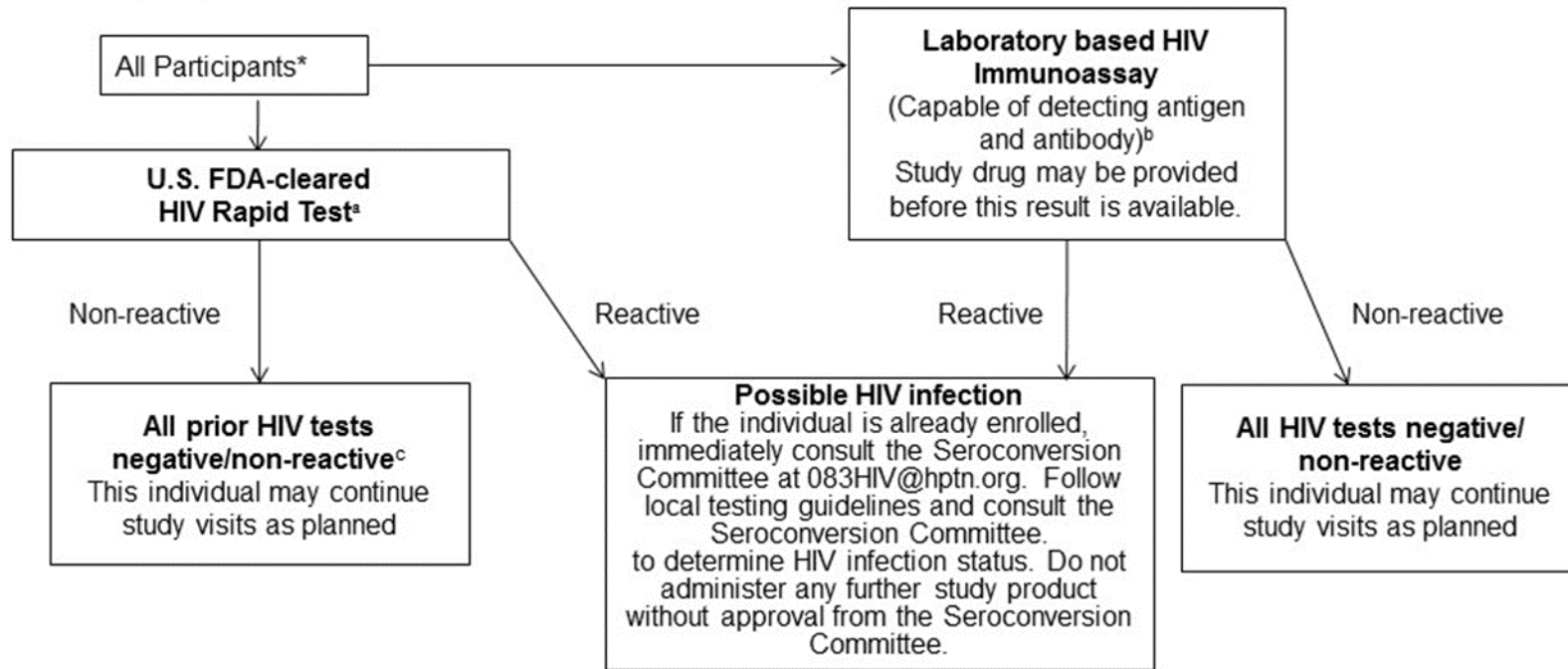
<sup>a</sup> If acute HIV infection is suspected, do not enroll the participant or administer study product at this time. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

<sup>b</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>c</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>d</sup> Before providing study drug, the site must ensure that the HIV rapid test from the Enrollment visit, and all HIV results from the Screening visit are available and are negative or non-reactive.

### HIV Testing Algorithm for Follow up Visits



**NOTES:**

<sup>a</sup> If acute HIV infection is suspected, do not administer any further study product. Immediately consult the Seroconversion Committee. In addition to following the algorithm above, the site should send a sample for an RNA test that, in the opinion of the site investigator, is able to detect early HIV infection. If possible, the site should use an assay that is FDA-cleared for early HIV diagnosis, such as the APTIMA HIV-1 RNA Qualitative Assay. The site should contact the Seroconversion Committee (083HIV@hptn.org) for additional guidance once all of the test results from this visit (including the HIV RNA test) are available.

<sup>a</sup> Sites that are not able to obtain HIV rapid test kits that are cleared by the US FDA may seek approval from the HPTN LC to use an alternate kit.

<sup>b</sup> This testing must be performed using a laboratory based, non-rapid HIV immunoassay that detects both HIV antigen and HIV antibody (either a 4<sup>th</sup> generation or 5<sup>th</sup> generation assay).

<sup>c</sup> At any visit where study product will be given, the site must ensure that the HIV rapid test from this visit, and all HIV results from prior study visits are negative or non-reactive.



**Revisions 13** Appendix II: Schedule for Additional Procedures for Enrolled Participants who have a Reactive or Positive HIV Test Result (including HIV confirmatory visit)

The following note has been added under Note 1 in the appendix.

**Note 2: Procedures for discordant or discrepant HIV test results are outlined in the SSP.**

**Revisions 14 a - c** Revisions to Appendix III: Toxicity Management

**14a.** Under “Toxicity Management General Guidance”

Grade 3

Participants who develop a Grade 3 AE or toxicity that is not specifically addressed in the Table below and is judged to be related to study product by the Investigator, study product use should be temporarily discontinued in consultation with the CMC. In general, and unless otherwise decided in consultation with the CMC, the investigator should re-evaluate the participant until resolution of the toxicity. For Grade 3 AEs deemed related to study product, the study product should be permanently discontinued if improvement to severity  $\leq$  Grade 2 cannot be documented within 4 weeks of receipt of the initial result. If study product is resumed and the same Grade 3 AE recurs at any time, the Investigator must consult the CMC for further guidance on holding of study product, frequency of reevaluation or progression to permanent discontinuation of the study product. For Grade 3 AEs deemed unrelated to study product, the CMC should be consulted for further management recommendations. **Additionally, for Grade 3 or higher abnormalities at Week 0 (study enrollment), consult the CMC for guidance regarding follow up and ongoing study product administration.**

**14b.** General Criteria for Discontinuation of Study Product

Note: The last paragraph under the “General Criteria for Discontinuation of Study Product” has been revised and is included 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 for HIV testing ~~only~~ until ~~the~~ **all participants complete conclusion of** Step 2 of the study. All such cases must be reported to the CMC.

**14c.** Guidance on Toxicity Management for Specified Toxicities: Creatinine Phosphokinase (CK or CPK)

Note: Only the creatinine phosphokinase has been revised and is included below.

**Creatine Phosphokinase (CK or CPK)**

CONDITION AND SEVERITY <sup>1</sup>	STUDY PRODUCT USE	FOLLOW-UP AND MANAGEMENT
<b>Creatine Phosphokinase</b>		
Grade 3	Continue study product until repeat test results are available	A Grade 3 or higher elevation in CPK should result in a repeat assessment within <u>2-4</u> weeks to ensure the result is transient or due to exercise and will not require a change in study treatment. A history regarding use of products known to cause increase of CPK (such as statins) physical activity or exercise preceding the CPK evaluation should be obtained.
Grade 4	Continue study product until repeat test results are available <del>if the elevation is thought to be possibly or probably related to study product.</del>	Grade 4 elevations in CPK should have a repeat assessment <b>within 2 weeks at least 24 hours</b> after the subject has abstained from exercise <del>for &gt;24 hours</del> . For persistent Grade 4 CPK elevations that are <b>symptomatic (myalgias, muscle pain, dark urine, or clinically significant changes in creatinine clearance, defined in consultation with the CMC) should have study product discontinued. Otherwise, the CMC will provide guidance on frequency of additional CPK monitoring.</b> <del>considered possibly or probably related to the study product, study product should be discontinued and the participant should be followed on study/off study product.</del>

**Revisions 15 a - d** Revisions to Appendix IV: Sample Screening and Enrollment Informed Consent Form

**15a.** Note: The following sentence has been added just below the last bullet and before the last paragraph under Step 3.

**It may be necessary for additional visit(s) and procedures in the event of unforeseen or unanticipated results; for example, you may have a side effect that requires repeat testing on your blood to ensure that the study drugs continue to be safe for you to use. Or, sometimes the results of some tests are not clear and additional testing is needed in order to confirm a test result. There also may be difficulties in sample shipping, processing, or testing; and/or if**

**you are experiencing any symptoms or changes in your physical condition. In the event of any of these unforeseen or unanticipated results, we will explain to you what will happen and what procedures will need to be done.**

**15b.** Note: The section below is new and appears after the description of procedures for Step 3, and before the section called “If you become injected with HIV during the study”.

### **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. If this happens, you would not get shots, and we would ask you to attend a visit once a year while Step 2 of the study is still ongoing 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 of the study is still ongoing in order to test you for HIV.**

**The procedures for these visits every year while Step 2 of the study is still ongoing are:**

- **Confirm where you live and how to contact you.**
- **Talk with you about HIV and ways to protect yourself from getting it.**
- **Give you a brief physical exam.**
- **Collect ~XX mL (about x teaspoons) of blood for HIV testing, the amount of the study drug in your blood, and for storage.**
- **Give you condoms and lubricant.**

**15c.** Note: Only the first paragraph of this section is impacted and depicted below.

## **RISKS AND/OR DISCOMFORTS**

### **Study Medications**

**The side effects of cabotegravir include:**

**Headaches, diarrhea, and fatigue. With the CAB that you get as a shot, people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising where they got the shot. Other reported side effects include muscle aches, nausea, fever and dizziness.**

- Headache
- Diarrhea
- Fatigue

- Muscle aches
- Nausea
- Fever
- Dizziness
- **Runny nose**
- **Sore throat**
- **Upper respiratory tract infection**
- **Vomiting (being sick)**
- **Difficulty sleeping**
- **Abnormal dreams/nightmares**
- **Depression**
- **Flatulence (gas or wind)**
- **Increase in the level of enzymes in the muscles (creatine phosphokinase)**
- With the CAB that you get as a shot, **some** people in other studies have said they had pain, irritation, skin redness, bumps, swelling, itching, bruising in the area where they got the shot, **some of which lasted a few weeks before resolving.**

**15d.** Note: The following text appears under the “CONFIDENTIALITY” section.

Your records may be reviewed by:

- US FDA
- US NIH
- US Department of Health and Human Services (DHHS), Office of Human Research Protection (OHRP)
- [insert names of applicable IRBs/ECs/other local review bodies as applicable]
- Study staff
- Study monitors
- Companies that makes the study drug (ViiV Healthcare and Gilead Sciences, Inc.)
- **Other U.S., local, and international regulatory entities may also review study records**