

Letter of Amendment #3 to:

**HPTN 082: Uptake and adherence to daily oral PrEP as a primary prevention strategy for young African women: A Vanguard Study
Version 1.0, 8 December 2015
DAIDS Document ID: 12068**

LoA #3: 15 October 2017

The following information impacts the HPTN 082 study and must be forwarded to all responsible Institutional Review Boards (IRBs) as soon as possible for their information and review. This Letter of Amendment must be approved by all responsible IRBs before implementation.

The following information does not impact the sample informed consents. Your IRB will be responsible for determining the process of informing subjects of the contents of this letter of amendment (LoA).

Upon receiving final IRB and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB correspondence should be retained in the site's regulatory files.

If the HPTN 082 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

Summary of Revisions and Rationale

1. Revisions were made to Sections 4.6.6 and 5.12 and Appendix 1C to collect drug level and creatinine clearance data from participants who have accepted PrEP but later decide to decline PrEP.
2. Revisions were made to section 5.13. If oral PrEP is stopped because a participant has a reactive/positive HIV test and subsequent site testing indicates that the participant is not likely to be infected, re-initiation of PrEP may be considered. Further testing must be performed at the study site and at the HPTN LC to determine HIV status as described below.
3. Section 5.15 was revised to allow participants to resume PrEP if they were no longer pregnant.
4. Section 6.9 was revised to harmonize the language with 6.6 on expedited adverse events to clarify that only SAEs deemed related to study drug need to be reported to DAIDS in an expedited manner.
5. A protocol signature page has been added for LoA #3.

Implementation of the Protocol Modification

The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. Deletions to the protocol text are indicated by ~~strike through~~; additions are indicated in **bold**.

Revision 1

4.6.6. Toxicity Management

The site investigator has the discretion to interrupt FTC/TDF at any time if s/he feels that continued medication use would be harmful to the participant or would interfere with treatment deemed clinically necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow-up will be documented, and the research associate or clinician will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing if indicated. All participants reporting an adverse event (AE) Grade 3 or higher will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at Screening/Enrollment) or stabilizes. PrEP will be discontinued if the CrCl decreases below 60 ml/min and serum creatinine will be monitored. All participants who discontinue PrEP (either for toxicity reasons or personal choice) will be followed under the procedures identified in Appendix IB for PrEP decliners— **except that DBS and creatinine levels should be collected at the first follow-up visit after PrEP discontinuation (see Section 5.12).**

5.12. Procedures for Participants who accept **or decline** PrEP after Enrollment (Late acceptors/**Late decliners**)

Late acceptors: Participants who decline PrEP at Enrollment but accept PrEP during a later visit will follow these additional procedures at this visit:

5.12.1. Administrative and Behavioral Evaluations/Procedures

- Study drug supply
- Randomization (to receive drug level feedback 4 and 8 weeks later or not)
- Adherence support (see Section 4.3)

5.12.2. Clinical Evaluations/Procedures

- Symptom directed physical exam

5.12.3. Laboratory Evaluations/Procedures

- Serum creatinine (for creatinine clearance)
- Screening for signs of acute HIV infection

Note that these are additional procedures, HIV testing and other procedures should also be completed per their usual visit schedule. If safety evaluations (creatinine clearance or HIV testing) are not available same day at site, drug supply should be held until after results are available. These women will then follow the schedule of evaluations for PrEP acceptors at all subsequent visits, without change to their visit schedule except as noted in Section 4.3 (Adherence Support for PrEP Acceptors). ~~For Late PrEP acceptors randomized to receive drug level feedback will be asked to return to the clinic 4 weeks after PrEP is dispensed for a blood draw, 4 weeks after that for counseling, and so on.~~

Late decliners: Participants who accept PrEP at Enrollment or in follow-up but decline PrEP during a later visit will follow these additional procedures at this visit:

5.12.4. Laboratory Evaluations/Procedures

- Serum creatinine (for creatinine clearance)
- DBS for storage

Appendix IC: Additional procedures at the PrEP initiation/**cessation** visit for those who accept/**decline** PrEP after enrollment

Participants who initially decline PrEP at enrollment will be offered PrEP throughout follow up. Participants who discontinue PrEP for any reason should also follow these procedures to ensure they may safely begin PrEP.

Administrative and Behavioral Evaluations/Procedures	
Study drug supply	X
Randomization	X
Adherence support (see Section 4.3)	X
Clinical Evaluations/Procedures	
Symptom-directed physical exam	X
Laboratory Evaluations/Procedures	
Creatinine clearance	X
Screening for signs of acute HIV infection and HIV testing	X

Participants who accept PrEP at enrollment or in follow up but decline PrEP during a later visit should complete the following procedures at their first visit after ceasing PrEP.

Laboratory Evaluations/Procedures	
Creatinine clearance	X
DBS for storage	X

Revision 2

5.13. Procedures for Participants with Suspected or Confirmed HIV Infection

Participants with a reactive or positive HIV test result identified at any time after study Enrollment will have further testing to confirm infection, as described in the SSP Manual, and will be referred for care. Appendix ID describes procedures for participants with suspected or confirmed HIV infection. **In all cases, participants should be placed on temporary product**

hold pending the results of testing. The site should notify the HPTN LC and Site IoR that a reactive/positive test result was obtained and should report all local HIV test results from this visit to the HPTN LC as soon as they are available. The site should schedule a confirmatory visit 1-2 weeks after this visit. In all cases, confirmation of HIV infection requires HIV testing at two separate study visits.

5.13.1 Procedures for HIV Confirmatory Visits

The following procedures will be conducted during a visit to confirm HIV infection:

Administrative Evaluations

- Update locator information
- Linkage to HIV care

Clinical Procedures:

- Symptom-directed physical exam
- Blood collection

Laboratory Evaluations/Procedures

- HIV testing (see SSP Manual)
- CD4 cell count testing
- Additional plasma storage*
- HIV genotyping for resistance testing*

** Stored plasma will be used for Quality Assurance (QA) testing, HIV viral load, and other assessments at the HPTN LC, including resistance testing (see Section 9). These assessments will be performed retrospectively; results will not be returned to study sites or participants (with the possible exception of HIV diagnostic testing, if results obtained at the HPTN LC differ from site results). Additional samples from participants with confirmed HIV infection will be collected and sent to a local laboratory for resistance testing to assist with clinical management; results from resistance testing performed in local laboratories will not be reported to the HPTN SDMC.*

Many of these procedures will be repeated 3 months later at a post-confirmatory visit with the exception of HIV genotyping. See Appendix ID.

~~If participants have a reactive or positive HIV test after study Enrollment, but further testing indicates that they are not HIV infected the participant may not resume study drug and will be terminated from the study.~~

If confirmatory testing indicates that a participant is HIV infected, study drug should be permanently discontinued, the participant should be terminated from the study following a 3 month post-confirmatory visit, and she will be referred for HIV care and treatment.

5.13.2 Additional Procedures for Participants with Inconclusive HIV Test Results

If a participant has a reactive or positive HIV test after study Enrollment, but other test results from that visit indicate that the participant may not be infected, further testing should be done to determine their HIV status. These participants should be placed on temporary product hold until the following testing is performed and results from all tests are reviewed by the HPTN LC and CMC. PrEP may be restarted in selected cases, as outlined below.

First re-visit:

This visit should occur 1-2 weeks after the visit where the first reactive/positive HIV test was obtained. This visit is the same as the confirmatory visit, but includes additional procedures. In addition to procedures described above (confirmatory visit, see Section 5.13.1), samples from this visit and the prior visit should be shipped to the HPTN LC for expedited testing (the HPTN LC will provide instructions for sample shipping). Local HIV testing at this visit should be performed under the direction of the HPTN LC, in consultation with the Protocol Chair(s) and Site IoR. All local HIV tests from this visit should be reported to the HPTN LC as soon as they are available.

If site testing at the first re-visit confirms that the participant is infected, study drug should be permanently discontinued, the participant should be terminated from the study following a 3 month post-confirmatory visit, and she will be referred for HIV care and treatment.

If all HIV tests at the first re-visit are negative/non-reactive, or if HIV test results from this visit are discrepant/discordant, the site should schedule a second re-visit to occur 2-3 weeks after this visit (see below).

Second re-visit:

This visit should occur at least 4 weeks after the visit where the first reactive/positive HIV test was obtained. Local HIV testing at this visit should be performed under the direction of the HPTN LC, in consultation with the Protocol Chair(s) and Site IoR, to facilitate clinical management of the participant. All local HIV test results from this visit should be reported to the HPTN LC as soon as they are available.

Consideration of restarting PrEP:

If the HIV test results indicate that it is unlikely that a participant is infected and the participant wishes to restart PrEP, the test results from all three visits (first reactive/positive visit, first re-visit, second re-visit) will be reviewed by the CMC, which includes the Protocol Chairs, the Site IoR, a representative from the HPTN LC, and DAIDS MO. The CMC will decide whether PrEP can be restarted. Reinitiation of PrEP will only be considered in the following cases 1): all HIV test results from the first and second re-visits are negative/non-reactive, or 2) a single HIV screening assay is reactive at one or more visits, with all other HIV tests negative/non-reactive. CMC approval is required in all cases before PrEP can be restarted. If PrEP is restarted, the participant should follow all scheduled visits and procedures.

If a reactive/positive HIV test is obtained after restarting PrEP study drug should be permanently discontinued. The participant should be counseled about HIV infection and referred for HIV care and treatment. The HPTN LC should be notified of the test results. Further HIV testing should be performed at the direction of the HPTN LC. The participant should remain in follow-up until HIV infection is confirmed, or the participant reaches the last study visit, whichever comes first.

Revision 3

5.15. Contraceptive Use and Pregnancy

Thus, while PrEP can be used in pregnancy, HPTN 082 will not continue women on PrEP if they become pregnant. Given the limited duration of follow-up in HPTN 082 (12 months), limited experience with PrEP use in younger African women and no existing protocols to formally evaluate PrEP use through pregnancy, women in HPTN 082 will be discontinued from PrEP at the time pregnancy is diagnosed. Women will continue to be followed off PrEP until **the end of pregnancy (confirmed negative pregnancy test) or until their Exit visit. Participants may restart PrEP after they are confirmed not to be pregnant through a negative pregnancy test.** At each visit after pregnancy is diagnosed, the procedures for PrEP decliners (e.g. SOC, Appendix IB) will be followed per their appropriate visit including STI testing and treatment as determined by the clinician. After their Exit visit, they will be followed clinically for pregnancy outcome.

Revision 4

6.9. Reporting Requirements for this Study

For each study participant, the SAE/EAE reporting period begins at Enrollment (Day 0) and ends when the participant's follow-up in the study ends (at the Week 52 Visit). All reportable SAEs (**related to study drug per Section 6.6**) occurring during the study reporting period will be reported to the principal investigator. ~~and for~~ EAEs (**including reportable SAEs only**) **should be reported** to the DAIDS RSC Safety Office in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the DAIDS EAE Manual). After the study has ended, sites must report Suspected Unexpected Serious Adverse Reaction (SUSARs) as defined in Version 2.0 of the DAIDS EAE Manual if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

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Final Version 1.0/ 8 December 2015

**Letter of Amendment #3
Dated October 15, 2017**

LETTER OF AMENDMENT SIGNATURE PAGE

I will conduct the 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 U.S. 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.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.”

Signature of Investigator of Record

Date

**Name of Investigator of Record
(printed)**