HIV Prevention Trials Network

LETTER OF AMENDMENT #2 TO:

HPTN 076
Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre-Exposure Prophylaxis (PrEP),
Version 2.0, dated 1 October 2014
DAIDS Protocol #: 11944

Date of Letter of Amendment: 13 March 2015

The information contained in this Letter of Amendment (LoA) impacts the HPTN 076 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their review and approval. This LoA must be approved by all responsible IRBs/ECs before implementation.

The information in this LoA impacts the Sample Screening and Enrollment Informed Consent Form.

Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, your site should implement the LoA immediately. Your site is still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Your site 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/EC correspondence should be retained in the site's regulatory files.

If the HPTN 076 protocol is amended in the future, this LoA will be incorporated into the next version.

Summary of Revisions and Rationale

The HPTN 076 protocol v2.0, 1 Oct 2014 has been updated to reflect the changes listed in this Summary of Revisions and Rationale. All changes made are clearly indicated in the next section, Implementation of the Protocol Modifications.

1) The protocol is being updated to permit serum/plasma pregnancy testing, in addition to the originally specified urine pregnancy testing.

Implementation of the Protocol Modifications

All additions are in **bold** type, and deletions appear as ~~strike-through~~, and each is highlighted in yellow for ease of reference.

Revision 1- Related Changes: Adding Serum/Plasma Pregnancy Testing as an Option

Revision 1, Change 1) Section 3.1.1, Inclusion Criteria for the Tissue Subset (US Sites Only):
"Participants must not be pregnant at the time of vaginal sampling, based on pregnancy test results from previous visits and on the result of ~~urine~~ pregnancy test performed on the same day before the proposed vaginal sampling."

Revision 1, Change 2) Section 6.1, Screening Visit:

- "~~Urine p~~ **P**regnancy testing **(see Section 10.1)***"

"*** Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Women not of childbearing potential are excluded from pregnancy testing throughout their participation in this study.**"

Revision 1, Change 3) Section 6.2, Section 6.3.1, Section 6.4, Section 6.5, Section 6.6, Section 6.7, Section 6.7.2, Section 6.8, and Section 6.9:

- "~~Urine p~~ **P**regnancy testing **(see Section 10.1)**"

Revision 1, Change 4) Section 6.5 and Section 6.7:

- "Study product will NOT be administered if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the ~~urine~~ pregnancy test performed at this visit."

Revision 1, Change 5) Section 6.7.1, Week 12 Enrollment Visit for the Tissue Subset Only (US Sites):
"Administrative and Counseling Procedures

- Review results of coagulation and Pap test results, if indicated (documentation of prior Pap results, or results obtained after the Week 6 visit).
- Review history to ensure participant has not missed injection visits.
- Review ~~urine~~ pregnancy results from prior visits and the ~~urine~~ pregnancy test result from this visit.
- If coagulation is normal, Pap test results are normal, ~~urine~~ pregnancy results from prior visits and the ~~urine~~ pregnancy test result from this visit are negative, and the participant has not missed injections then enroll in the Tissue Subset."

Revision 1, Change 6) Section 6.8, Weeks 36 and 44 Visits (Injection Vists):

- "Fluid samples will NOT be collected if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the ~~urine~~ pregnancy test performed at this visit.
- Study product will NOT be administered if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the ~~urine~~ pregnancy test performed at this visit."

Revision 1, Change 7) Section 6.8.1, Biopsy Visit for the Tissue Subset Only (US Sites):

- "Tissue samples will NOT be collected if the participant is pregnant. This must be based on pregnancy test results from previous visits and on the result of the ~~urine~~ pregnancy test performed at this visit."

Revision 1, Change 8) Section 10.1, Local Laboratory Specimen Processing:

- "~~Urine p~~ **P**regnancy testing [a]"

"Pregnancy testing
All women of reproductive potential will have a ~~urine~~ βHCG test for pregnancy (sensitivity of ≤ 25 mIU/mL) at the majority of visits. **Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Testing may be performed using a urine, plasma, or serum sample.** Continued pregnancy testing is not required following an initial positive test result. It will be repeated after pregnancy completion and must have returned to normal prior to recommencement of study product."

Revision 1, Change 9) Appendix I, Schedule of Study Visits and Procedures, Schedule I:

~~Urine p~~ **P**regnancy test[3,4]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	X

"(4) **Pregnancy testing may be performed in the clinic or the laboratory at all visits where this testing is indicated. Testing may be performed using a urine, plasma, or serum sample. The assay used for pregnancy testing must have a limit of detection of 25 mIU/mL or lower. Women not of childbearing potential are excluded from pregnancy testing throughout their participation in this study.** Pregnancy testing is not required at subsequent visits if a positive result is obtained."

Revision 1, Change 10) Appendix I, Schedule of Study Visits and Procedures, Schedule II:

Prior to Enrollment, review ~~urine~~ pregnancy results from prior and current visits [3]											X							

Revision 1, Change 11) Appendix III, Informed Consent Template, Sample Screening and Enrollment Informed Consent Form, What happens during the Screening Visit?:

- "We will ask you for a urine sample. ~~We will test your urine to see if you are pregnant.~~
- Your samples (blood and urine) will be tested **to see if you are pregnant and** to assess you for any sexually transmitted infections. Your blood and urine will be tested to assess your overall health, and to see if your liver and kidneys are working normally."

Revision 1, Change 12) Appendix III, Informed Consent Template, Sample Screening and Enrollment Informed Consent Form, has been revised at the following visits:

- Visit #1: Enrollment Visit
- Visits #2-6: First 2 Weeks
- Visit #7: Week 4
- Visits #8, 9 & 11: Weeks 6, 8, and 14
- Visits #10, 12-15: Weeks 12, 20, 28, 36, and 44:
- Visits #16-18: Weeks 52, 64 and 76

as follows:

- "We will ask you for a urine sample. ~~We will test your urine to see if you are pregnant.~~
- Your blood and urine will be tested to assess your overall health, **to see if you are pregnant** and to see if your liver and kidneys are working normally."