HIV Prevention Trials Network

LETTER OF AMENDMENT #1 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: 3 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 does not impact the Sample 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 a 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) Adverse Events (AEs) will be graded using the updated Division of AIDS/NIAID/NIH Toxicity Tables released on 06 February 2015. The updated tables, Version 2.0, dated November 2014, will be used for the entire duration of this study.

Implementation of the Protocol Modifications

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 ~~strikethrough~~; additions are indicated in **bold**.

Revision 1- Related Changes: Incorporating Updated DAIDS Toxicity Tables

Revision 1, Change 1) Section 3.1.1, Inclusion Criteria for the Tissue Subset (US Sites Only), page 14 has been revised as follows:

> "Satisfactory Pap results in the 12 calendar months prior to biopsy consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version **2.0, November 2014,**~~1.0, December 2004 (Clarification dated August 2009),~~ or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to biopsy is required, as indicated."

Revision 1, Change 2) Section 7.2.1, Adverse Event, page 39 has been revised as follows:

> "Study site staff will document in source documents and the appropriate AE Log CRF all AEs reported by or observed in enrolled 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.**~~1.0, December 2004 (Clarification dated August 2009).~~"

Revision 1, Change 3) Section 8.2.1, Primary Endpoint, page 42 has been revised as follows:

> "Consistent with the primary study objective to evaluate the safety of the injectable product, TMC278 LA, (1200 mg dose administered at Weeks 4, 12, 20, 28, 36 and 44), through 48 weeks after initial injection (at Week 52) in women in SSA and US, the primary safety endpoint is the proportion of participants in each arm experiencing any Grade 2 or higher clinical and laboratory AEs that occur from the initial injection to 8 weeks after the last injection (Week 52) among participants who receive at least one injection. Clinical and laboratory AEs are defined by the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version **2.0, November 2014.**~~1.0, Dec *2004*.~~"

Revision 1, Change 4) Appendix II, Section 14.1 Toxicity Management General Guidance, page 67

> "In general, the IoR has the discretion to hold study product at any time if s/he feels that continued product use would be harmful to the participant, or interfere with treatment deemed clinically necessary according to the judgment of the IoR. IoRs should consult the CMC for further guidance in restarting study drug or progressing to permanent

discontinuation. Revealing a participant's blinded status may occur only for individuals who seroconvert or in the event that knowledge of study drug is deemed critical to the management of a serious emergent medical condition of the participant. The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version ~~1~~**2**.0, dated **November, 2014** ~~December 2004 (with Clarification dated August 2009),~~ (which is available at the following website: http://rsc.tech-res.com/safetyandpharmacovigilance/) must be followed."

Revision 1, Change 5) Appendix II, Section 14.2.1 Nausea, Vomiting and Diarrhea, Toxicity Management Tables on pages 70-71

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Nausea		
Transient (< 24 hours) or intermittent **AND** ~~nausea with~~ no or minimal interference with oral intake (Grade 1) Persistent nausea resulting in decreased oral intake for 24 – 48 hours (Grade 2, un-related)	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
Persistent nausea resulting in decreased oral intake for 24 – 48 hours (Grade 2, related) Persistent nausea resulting in minimal oral intake for > 48 hours OR ~~Aggressive~~ rehydration indicated (e.g., IV fluids) (Grade 3) Life-threatening consequences (e.g., hypotensive shock) (Grade 4)	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Vomiting		
Transient or intermittent vomiting **AND** ~~with~~ no or minimal interference with oral intake (Grade 1) Frequent episodes ~~of vomiting~~ with no or mild dehydration (Grade 2, un-related)	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
Frequent episodes ~~of vomiting~~ with no or mild dehydration (Grade 2, related) Persistent vomiting resulting in orthostatic hypotension OR aggressive rehydration indicated (e.g., IV fluids) (Grade 3) Life-threatening consequences (e.g., hypotensive shock) (Grade 4)	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

CONDITION AND SEVERITY	IMMEDIATE ACTION	FOLLOW-UP AND MANAGEMENT
Diarrhea		
Transient or intermittent episodes of unformed stools OR increase of ≤ 3 stools over baseline per 24-hour period (Grade 1) Persistent episodes of unformed to watery stools OR increase of 4 – 6 stools over baseline per 24-hour period (Grade 2, un-related)	Continue study drug (reminder to take study drug with a meal during oral phase)	Treat symptomatically with hydration, oral antiemetic or antidiarrheal therapies, at the discretion of the IoR. The IoR should order any clinically relevant laboratory analyses (per judgment of the IoR).
Persistent episodes of unformed to watery stools OR Increase of 4 – 6 stools over baseline per 24-hour period (Grade 2, related) <br~~Bloody diarrhea OR~~ Increase of ≥ 7 stools per 24-hour period OR IV fluid replacement indicated (Grade 3) Life-threatening consequences (e.g., hypotensive shock) (Grade 4)	Discontinue study drug temporarily	Participants with Grade 2 nausea, vomiting, or diarrhea, for which an alternative etiology is not established, or Grade ≥ 3 must discontinue the study drug temporarily until Grade 1 or lower and be treated symptomatically. Should condition(s) not improve to Grade 1 within 7 days, the IoR should consult the CMC for guidance on continuing the temporary discontinuation or progressing to permanent discontinuation of study drug.

Revision 2, Change 6) Appendix II, Section 14.2.2 Clinical Hepatitis, Toxicity Management Table on pages 72-73

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Elevations in AST or ALT (New clinical finding or increase from baseline clinical finding only)		
1.25 – <2.5 x ULN (Grade 1)	Continue study drug unless participant is symptomatic	Participants may enter the study with ≤ 2 x ULN transaminase elevations. If a new elevation occurs, AST or ALT should be repeated in one week. Study drug may be continued while repeating AST and ALT at the discretion of the IoR provided the participant is asymptomatic. In the case of symptomatic participants, study drug will be held temporarily, and management (including resumption of study drug) should be arranged in consultation with the CMC.

2.5~~6~~ – <5.0 x ULN (Grade 2)	Continue study drug unless participant is symptomatic	Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results) and then be followed weekly until levels are ≤ 2 x ULN transaminase. The frequency of follow up may be altered at the discretion of the site IoR if deemed to be unrelated to study product following consultation with the CMC. Study drug may continue at the discretion of the IoR provided the participant is asymptomatic. In the case of symptomatic participants or if thought to be study drug related, study drug will be held temporarily., and management (including resumption of study drug) should be arranged in consultation with the CMC.
5.0~~1~~ – <10.0 x ULN (Grade 3)	Discontinue study drug temporarily	Study drug should be temporarily held for any Grade 3 AST or ALT. Participants should have AST/ALT re-checked as soon as possible (ideally within 1 week of the receipt of the results). Participants should then be followed weekly until levels are ≤ 2 x ULN transaminase. Resumption of study drug should be arranged in consultation with the CMC. If improvement to Grade ≤1 cannot be documented within three weeks of receiving the Grade 3 results, study drug must be permanently discontinued. If following a Grade 3 event(s) the participant is permitted to resume study drug, but has an additional event (AST and/or ALT) at a Grade 3 level, the IoR must permanently discontinue the study drug, offer symptomatic treatment (if appropriate), and order any clinically relevant laboratory analyses (per judgment of the IoR).
≥ 10.0 x ULN (Grade 4)	Permanently discontinue study drug	Study drug should be permanently discontinued for any Grade 4 AST or ALT and the CMC should be immediately notified. Participants should have AST/ALT re-checked as soon as possible (at most within 1 week of the receipt of the results). Participants should then be followed weekly until levels are ≤ 2 x ULN transaminase unless indicated by the CMC.

Revision 1, Change 7) Appendix II, Section 14.2.3 EKGs: Measurement of QTcF, Toxicity Management Table on pages 73-74

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Prolonged QTcF		
~~Asymptomatic, QTcF interval~~ 0.45 – 0.47 sec ~~OR Increase interval < 0.03 sec above baseline~~ (Grade 1)	Continue	None required.

~~Asymptomatic, QTcF interval~~ >0.47~~8 –~~ 0.5~~0~~49~~ sec ~~OR Increase in interval 0.03 – 0.05 sec above baseline~~ (Grade 2)	Temporarily discontinue	Temporarily discontinue and consult with CMC if deemed to be study drug related. Repeat EKG in 48 hours.
~~Asymptomatic, QTcF interval ≥~~ >0.50 sec OR ~~Increase in interval~~ ≥ 0.06 sec above baseline (Grade 3)	Permanently discontinue	Repeat EKG within 48 hours. If prolongation confirmed, stop all study products permanently. Treat symptoms appropriately. Notify CMC.
Life-threatening consequences~~,~~ (e.g. Torsade de pointes, ~~or~~ other associated serious ventricular dysrhythmia) (Grade 4)	Permanently discontinue	If detection of 4+ QTcF at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC

Revision 1, Change 8) Appendix II, Section 14.2.4 Acute Systemic Allergic Reaction, Toxicity Management Table on pages 74-75

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Acute Systemic Allergic Reaction		
Localized urticaria (wheals) with no medical intervention indicated (Grade 1)	Continue	May treat symptomatically. Review within 48 hours if thought to be study drug related and advise participant to return if any worsening.
Localized urticaria with ~~medical~~ intervention indicated OR Mild angioedema with no ~~medical~~ intervention indicated (Grade 2)	Continue or interrupt study drug if deemed unrelated to study medication at discretion of IoR and consult with CMC. If deemed to be study drug related temporarily withhold study product and consult with CMC.	Treat symptomatically as required. May require temporary withdrawal of study product. Inquire for possible alternative causative agents. Drug can be recommenced after consultation with CMC. Treat symptoms. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Generalized urticaria OR Angioedema with ~~medical~~ intervention indicated OR Symptomatic mild bronchospasm (Grade 3)	Permanently discontinue	If detection of 3+ systemic reaction at any visit, study drug should be permanently discontinued. Inquire about other alternative causative agents. Treat symptoms appropriately. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). Notify CMC.
Acute anaphylaxis OR Life-threatening bronchospasm OR laryngeal edema (Grade 4)	Permanently discontinue	If detection of 4+ systemic reaction at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Revision 1, Change 9) Appendix II, Section 14.2.5 Injection Site Reactions, Toxicity Management Table on pages 75-76

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Injection site reactions		
Pain ~~/~~ **or** tenderness causing no or minimal limitation **of use of limb** (Grade 1)	Continue	May treat symptomatically.
Pain ~~/~~ **or** tenderness causing greater than **minimal limitation of use of limb** ~~interference with usual social & functional activities~~ (Grade 2)	Continue in consultation with CMC	Treat symptomatically as required.
Pain ~~/~~ **or** tenderness causing inability to perform usual social & functional activities (Grade 3)	Continue or interrupt study drug at discretion of IoR and consult with CMC	Treat symptomatically as required. May require temporary withdrawal of study product. Drug can be recommenced after consultation with CMC. Treat symptoms.
Pain ~~/~~ **or** tenderness causing inability to perform basic self-care function OR Hospitalization **indicated** ~~(other than emergency room visit) indicated for management of pain/tenderness~~ (Grade 4)	Permanently discontinue	If detection of 4+ IS reaction at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC.

~~Erythema OR Induration of 5x5 cm – 9x9 cm (or 25 cm2 – 81cm2)~~ **2.5 to <5.0 cm in diameter OR 6.25 to <25cm^2 surface area AND Symptoms causing no or minimal interference with usual social activities** (Grade 1)	Continue	May treat symptomatically.
~~Erythema OR Induration OR Edema > 9 cm any diameter (or > 81 cm2)~~ **≥ 5 to < 10cm in diameter OR ≥25 to <100cm^2 surface area OR Symptoms causing greater than minimal interference with usual social & functional activities** (Grade 2)	Continue in consultation with CMC	Treat symptomatically as required.
~~Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage~~ **≥ 10cm in diameter OR ≥ 100cm^2 surface area OR Ulceration OR Secondary infection OR Phlebitis OR Sterile abscess OR Drainage OR Symptoms causing inability to perform usual social & functional activities** (Grade 3)	Interrupt study drug at discretion of IoR and consult with CMC	Treat symptomatically and refer for further surgical management as required.
~~Necrosis involving dermis and deeper tissue~~ **Potentially life-threatening consequences (e.g., abscess, exfoliative dermatitis, necrosis involving dermis or deeper tissue)** (Grade 4)	Discontinue	Treat symptomatically and refer for further surgical management as required.

Revision 1, Change 10) Appendix II, Section 14.2.6 Rash, Toxicity Management Table on pages 77-79

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT

Skin rash		
Localized ~~macular~~ rash (Grade 1)	Continue unless management states otherwise	A finding of 1+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). Additional safety blood samples are to be taken <u>if</u> the participant's AST/ALT on Day zero <u>and/or</u> Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression. Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement. If so, drug should be held and CMC consulted. Review within 48 hours and advise participant to return urgently if worsening of rash.
Diffuse ~~macular, maculopapular, or morbilliform~~ rash OR Target lesions (Grade 2)	Temporarily hold study drug as per follow-up and management	A finding of 2+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). Additional safety blood samples are to be taken <u>if</u> the participant's AST/ALT on Day zero <u>and/or</u> Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression. Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement. If any present, drug should be held and CMC consulted. Review within 48 hours and advise participant to return urgently if worsening of rash.

Diffuse ~~macular, maculopapular, or morbilliform~~ rash ~~with and~~ **AND** vesicles or limited number of bullae ~~OR~~ **or** superficial ulcerations of mucous membrane limited to one site (Grade 3)	Permanently discontinue	If detection of 3+ or greater skin rash at any visit, study drug should be permanently discontinued regardless of serum or plasma LFTs and CMC contacted immediately. A finding of 3+ skin rash should be treated symptomatically. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count). Additional safety blood samples are to be taken if the participant's AST/ALT on Day zero and/or Day one of rash > two x baseline value, and/or ≥ five x ULN and/or in case of rash progression. Weekly follow-up visits are required (or more frequently at the IoR's discretion) as long as Grade 3-4 rash is present. Participant should be examined for evidence of systemic involvement: fever, malaise or mucosal involvement. A dermatologic referral should be considered.
Extensive or generalized bullous lesions OR ~~Stevens-Johnson syndrome OR~~ Ulceration of mucous membrane involving two or more distinct mucosal sites OR **Stevens-Johnson syndrome OR** Toxic epidermal necrolysis ~~(TEN)~~ (Grade 4)	Permanently discontinue	If detection of 4+ or greater skin rash at any visit, study drug should be permanently discontinued regardless of serum or plasma LFTs and CMC notified immediately. A finding of 4+ skin rash is an emergency and must trigger a specialist referral or referral to an emergency center for possible admission and acute management. Inquiries should be made about other possible causative agents or conditions. Blood should be drawn for AST, ALT, and a CBC (including hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, monocytes, eosinophils, basophils, and platelet count).

Revision 1, Change 11) Appendix II, Section 14.2.7 Depression/Suicidality, Toxicity Management Tables on pages 79-80

CONDITION AND SEVERITY	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT
Depression/~~Suicidality~~		

~~Depression or mood alteration causing no or minimal interference with usual social & functional activities~~ **Symptoms with intervention not indicated OR Behavior causing no or minimal interference with usual social & functional activities** (Grade 1)	Continue	May treat symptomatically.
~~Depression or mood alteration causing greater than minimal interference with usual social & functional activities~~ **Symptoms with intervention indicated OR Behavior causing greater than minimal interference with usual social & functional activities** (Grade 2)	Continue or interrupt study drug at discretion of IoR and consult with CMC depending on relatedness to study product	Treat symptomatically as required. May require temporary withdrawal of study product. Inquire for possible alternative causative agents. Drug can be recommenced after consultation with CMC. Treat symptoms.
~~Depression or mood alteration causing inability to perform usual social & functional activities~~ **Symptoms with hospitalization indicated OR behavior causing inability to perform usual social & functional activities** (Grade 3)	Permanently discontinue	If detection of 3+ depression at any visit, study drug should be permanently discontinued. Treat symptoms appropriately. Notify CMC.
~~Behavior potentially harmful to self or others (e.g., suicidal and homicidal ideation or attempt, acute psychosis) OR Causing inability to perform basic self-care functions~~ **Threatens harm to self or to others OR Acute psychosis OR Behavior causing inability to perform basic self-care functions** (Grade 4)	Permanently discontinue	If detection of 4+ depression or suicidality at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC.
CONDITION AND SEVERITY	**STUDY DRUG USE**	**FOLLOW-UP AND MANAGEMENT**
Suicidality		

Preoccupied with thoughts of death AND No wish to kill oneself (Grade 1)	Continue	May treat symptomatically.
Preoccupied with thoughts of death AND Wish to kill oneself with no specific plan or intent (Grade 2)	Continue or interrupt study drug at discretion of IoR and consult with CMC depending on relatedness to study product	Treat symptomatically as required. May require temporary withdrawal of study product. Inquire for possible alternative causative agents. Drug can be recommenced after consultation with CMC. Treat symptoms.
Thoughts of killing oneself with partial or complete plans but no attempt to do so OR Hospitalization indicated (Grade 3)	Permanently discontinue	If detection of 3+ ~~depression~~ **suicidality** at any visit, study drug should be permanently discontinued. Treat symptoms appropriately. Notify CMC.
Suicide attempted (Grade 4)	Permanently discontinue	If detection of 4+ ~~depression or~~ suicidality at any visit, study drug should be permanently discontinued. Intervene urgently as appropriate. Refer for ongoing management after emergency treatment. Notify CMC.