LETTER OF AMENDMENT #02 TO:

MTN-003
DAIDS Document ID 10622

Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women

Version 1.0/22 May 2008
IND # 55,690

Letter of Amendment Date: March 26, 2010

Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB) and/or Ethics Committee (EC) as soon as possible for their information and review. Site IRBs/ECs are responsible for assessing whether and how the changes included below are communicated to study participants. All IRB/EC requirements must be followed. As this LoA does not impact the overall risk-to-benefit profile of study participation or the informed consent documents, re-consenting is unnecessary.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003. This LoA provides clarification on the following items:

1. Protocol Team Roster, to reflect updates to the Protocol Team
2. Study procedures, regarding results of assays from other MTN protocols for use in VOICE, to decrease participant and laboratory burden; and the frequency of the assessment of intravaginal practices, to resolve a discrepancy between the ACASI instrument and the protocol
3. Adverse event reporting requirements, to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS
4. Product use management, to avoid unnecessary product hold
5. Investigator guidance for clinical management of laboratory test results

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Implementation

This LoA is official MTN-003 protocol documentation. Prior to implementing revisions listed here, study sites will submit the LoA to all relevant regulatory authorities and IRB/ECs. The DAIDS Regulatory Affairs Branch will submit the LoA to the US Food and Drug Administration for inclusion in Investigational New Drug application # 55,690. Upon receiving final IRB/EC and any other applicable regulatory entity approval(s) for this LoA, sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Compliance Center (RCC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that the required LoA registration documents have been received and are complete. Sites will not be able to implement the changes related to EAE reporting requirements in this LoA until after they have received a LoA registration notification from the DAIDS PRO. All other sections of this LoA will be implemented immediately upon IRB/EC approval. A copy of the DAIDS PRO

LoA registration notification along with this LoA and any IRB/EC correspondence should be retained in the site's regulatory files. Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

1. The Protocol Team Roster is updated.

The following individuals have been added to the Protocol Team Roster:

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The following individuals are removed from the Protocol Team Roster: Anne Coletti, Nancy Connolly, Nicola Coumi, Nozizwe Dladla-Qwabe, Vijayanand Guddera, Laura McKinstry, Emilder Tazvivinga-Chihota, Francis Martinson, Nancy Padian, and Morenike Ukpong.

2. In Section 7, STUDY PROCEDURES, two edits are made.

A sentence is added at the end of the first paragraph in Section 7 to allow results from certain assays performed on the same day for other MTN studies to be used for VOICE.

Results from HIV rapid tests performed on the same day for other MTN studies may also be utilized for VOICE, provided the test kit and laboratory approved by MTN NL are the same for both studies, and the site has documented permission for this substitution from MTN NL.

Additionally, the frequency of assessment of intravaginal practices is modified in Section 7.5.1 and in Appendix I:

- Intravaginal practices assessment:
  - ~~Quarterly~~**Annually**
  - At PUEV
  - At Termination Visit

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR 1	SCR 2	ENR	MLY	QRT	SEM	ANN	PUEV	TERM
Intravaginal Practices Assess.					~~X~~	~~X~~	X	X	X

3. In Section 8, ASSESSMENT OF SAFETY, and Section 9, CLINICAL MANAGEMENT, text is edited to reflect updates to adverse event reporting. Of note, as of May 3, 2010, EAE reporting will follow revised guidelines included in the Manual for Expedited Reporting of Adverse Events to DAIDS, dated January 2010. The revised manual reduces the categories for relatedness from five to two (related

and not related), and mandates reporting of all SAEs to DAIDS, regardless of relatedness.

In Section 8.2, fifth paragraph, second bullet:

- The relationship of all AEs reported on CRFs will be assessed based on the Manual for Expedited Reporting of Adverse Events to DAIDS, dated ~~May 6, 2004~~ **January 2010** (DAIDS EAE Manual), the product Package Inserts and Investigators Brochures, and the clinical judgment of the IoR/designee. The study products that must be considered when AE relationship **is assessed** are TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

In Section 8.3, second paragraph:

EAE Reporting ~~Level~~
This study uses **the All SAEs category of** ~~the Standard Level of expedited~~ AE reporting as defined in the DAIDS EAE Manual**.** ~~, except that f~~**F**etal losses will not be reported as EAEs. Although not reported as EAEs, all fetal losses will be documented on case report forms and routinely reviewed by the PSRT and DSMB, as described in Section 8.1. After the Termination Visit, only pregnancy outcomes that meet criteria for EAE reporting (e.g., congenital anomalies) occurring among participants known to be pregnant at the Termination Visit will be reported.

In Section 8.3, third paragraph:

Study Agents for Expedited Reporting to DAIDS
The study agents that must be considered ~~in determining relationships of AEs requiring~~ **for** expedited reporting to DAIDS are: TDF tablet, FTC/TDF tablet, tenofovir 1% vaginal gel, and study gel applicator.

In Section 9.4, second paragraph:

Grade 3
Participants who develop a Grade 3 AE that is not specifically addressed below and is judged by the IoR/designee to be ~~probably not or~~ not related to study product may continue product use.

In Section 9.4, fifth paragraph:

Grade 4
A participant who develops a Grade 4 AE that is not specifically addressed below (regardless of relationship to study product) should have the study product held. The IoR/designee must consult the PSRT and continue the temporary product hold until a recommendation is obtained from the PSRT. In general, product use will not be resumed if the Grade 4 AE is considered ~~probably not, possibly, probably, or definitely~~ related to product use. If, in consultation with the PSRT, product use is resumed and the same Grade 4 AE recurs at Grade 4 level at any time, study product must then be permanently discontinued.

In Section 9.5.1, Nausea, Vomiting, and/or Diarrhea, under VAGINAL STUDY PRODUCT:

VAGINAL STUDY PRODUCT
Unless other temporary product hold requirements apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is ~~probably or definitely~~ related to vaginal study product. In this case, the IoR/designee must consult the

PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

In Section 9.5.2, AST and/or ALT Elevations, under VAGINAL STUDY PRODUCT:

VAGINAL STUDY PRODUCT
Unless other temporary product hold requirements apply, vaginal study product need not be held unless the IoR/designee has compelling evidence that the toxicity is ~~probably or definitely~~ related to vaginal study product. In this case, the IoR/designee must consult the PSRT for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

4. New text is added to the beginning of Section 9.3 to clarify product hold guidelines.

In general, product hold is not triggered by an AE deemed already resolved at the time of participant report or site discovery, according to the judgment of the IoR/designee. However, such an AE may trigger permanent discontinuation, if it is an AE recurrence specified by criteria below to result in permanent discontinuation of study product.

5. Text is edited in Section 9, CLINICAL MANAGEMENT, to provide guidance for management of laboratory test results.

In Section 9.5.2, AST and/or ALT Elevations, text is added under ORAL STUDY PRODUCT, fifth paragraph, first sentence:

Grade 4
Study product should be permanently discontinued **and the PSRT will be consulted**. The IoR/designee must follow the participant's ALT and AST at least weekly until levels are Grade ≤1.

In Section 9.5.3, Creatinine, text is added within ORAL STUDY PRODUCT:

ORAL STUDY PRODUCT
The IoR/designee should temporarily hold oral study product for any rise in creatinine greater than or equal to 1.5 x participant's baseline value (BL). The creatinine should be repeated as soon as possible (at most within 1 week). Product use may be resumed when the creatinine level improves to ≤ 1.3 x BL**, in consultation with the PSRT**. If product use is resumed and the creatinine level increases to ≥ 1.5 x BL, product use must be permanently discontinued.

In Section 9.5.6, Hypophosphatemia, text is edited within ORAL STUDY PRODUCT, Grades 3 and 4:

Grade~~s~~ 3 ~~and 4~~
The phosphate test should be repeated within 1 week of the receipt of the results**, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose; study product use may continue in the interim. If the participant does not have repeat testing within the specified time frame, PSRT consultation is required.** Intake of phosphate-rich food or fluid should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated. ~~During the time that supplemental phosphate is provided to the participant and the time that testing is repeated, sites should follow temporary product hold/permanent discontinuation guidelines described in Section~~

~~9.4. If improvement to ≤ Grade 2 can not be documented within one week of the receipt of the **confirmed** Grade 3 or 4 result, study product must be permanently discontinued.~~

In interpreting the results of testing accompanying the repeat phosphate test, sites should follow these guidelines:

- **Participants with proteinuria and/or glycosuria of ≥3+ will have oral study product held and require consultation with the PSRT for further testing and management.**
- **Participants with creatinine ≥ 1.5 x BL and/or creatinine clearance ≤ 50 mL/min, will have oral study product held, and will follow all additional management guidelines specific to the applicable adverse event noted in Sections 9.5.3 and 9.5.4.**

Participants who do not meet the above criteria may continue study product, with the following additional requirements:

- **Urine dipstick results of 1+ will be managed according to guidance in Sections 9.6 (for proteinuria) and 9.7 (for glycosuria).**
- **Findings of proteinuria and/or glycosuria of 2+ require consultation with the PSRT for the participant's further testing and management.**

For participants with a confirmed Grade 3 result, the following additional requirements apply:

- **Phosphate levels will be retested approximately weekly until return to ≤ Grade 2, unless other retesting schedule has been advised by the PSRT.**
- **The PSRT will be consulted for further testing and management if phosphate levels do not return to ≤ Grade 2 within two weeks of the receipt of a confirmed Grade 3 result.**

<u>Grade 4</u>

Study product will be held and the PSRT will be consulted. The phosphate test should be repeated within 1 week of the receipt of the results, and should be accompanied by serum creatinine testing and urine dipstick for protein/glucose. If the participant does not have repeat testing within the specified time frame, PSRT consultation is required. Intake of phosphate-rich food or fluid should be advised. Oral phosphate supplementation may be implemented at the discretion of the site investigator. Other causes of low phosphate should be investigated.

Participants will have phosphate levels retested approximately weekly until return to ≤ Grade 2, in consultation with the PSRT. Participants may resume study product, provided that:

- **Study product hold is not otherwise indicated (e.g., due to the results of creatinine, creatinine clearance, urine protein, and/or urine glucose)**
- **The phosphate level has returned to ≤ Grade 2**
- **A request to resume study product is approved by the PSRT**