

LETTER OF AMENDMENT #01 TO:

MTN-017

A Phase 2 Randomized Sequence Open Label Expanded Safety and Acceptability Study of Oral Emtricitabine/Tenofovir Disoproxil Fumarate Tablet and Rectally-Applied Tenofovir Reduced-Glycerin 1% Gel

Version 1.0 dated July 17, 2012

DAIDS Protocol ID: 11857

IND #73,382

Date of Letter of Amendment: 25 February 2013

Site Instruction

The following information impacts the MTN-017 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRB/EC before implementation. The following information impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this Letter of Amendment (LoA).

Implementation

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit a 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. A 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.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-017.

This LoA clarifies the reporting requirements for study product protocol deviations, management of PrEP during the Oral (Daily FTC/TDF) Period, corrects a typo for the clotting tendency blood test required for participants in the *PK, PD and Immunological Subset*, modifies the timing of AE resolution prior to the initiation of product in Periods 2 and 3, updates the PK sample collection schedule and the total amount of blood to be collected, and clarifies the planned sample collection for HSV 1/2. In addition, the protocol has been modified to remove CASI as a component of the Data Convergence Interview and adds available PK data as an additional element. The LoA removes the collection of sexual behavior and condom use data via text message, and clarifies that all AEs are to be recorded on CRFs. Other modifications include, adding the potential risk associated with sending and receiving text messages, adding to the Sample Informed Consent compensation for participants who reply to 85% or more of the study text messages and noting that both Adherence Counseling Sessions and Data Convergence Interviews will be audio-recorded and data will be analyzed for patterns of product use. Updates to the Protocol Team Roster and the Tenofovir Gel Investigator's Brochure reference have been included. Finally, other minor clarifications and corrections have been incorporated.

With the exception of protocol roster changes and relocation of blocks of text and changes that impact the entire protocol, text to be deleted is noted by ~~strike through~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

1. The following additions have been added to the Protocol Team Roster:

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2. For consistency and accuracy, throughout the protocol, the word 'tablet' will be used to describe oral FTC/TDF, rather than 'pill'.
3. A typographical error has been corrected within Exclusion Criteria number 3, letter i:

i. *PK, PD and Immunological Subset only*: International normalized ratio (INR) > 1.5x the site laboratory ULN or ~~partial thromboplastin~~ **Prothrombin** time (PTT) > 1.25x the site laboratory ULN

4. Protocol specific reporting requirements for protocol deviations are included within Section 6.4.5. A new second paragraph has been added:

A protocol deviation will be reported if no product use is conveyed for any given month, by participant report. Specific reporting details are provided in the MTN-017 SSP Manual available at www.mtnstopshiv.org.

5. The language within Section 6.5, *Adherence Counseling* has been relocated to Section 7.10.2, *Adherence* and the following has been inserted:

For study product adherence counseling details, please reference Section 7.10.2, *Adherence*.

6. Section 6.6, *Concomitant Medications and Practices*, first paragraph, new fifth sentence, added to provide guidance for participants prescribed PrEP:

During the Oral (Daily FTC/TDF) Period, any participant who is routinely using oral PrEP will use the study-provided FTC/TDF and will be advised to refrain from using their routine PrEP medication. Prescription medications, over-the-counter preparations, vitamins and nutritional supplements, and herbal preparations will be recorded as concomitant medications.

7. The following modification is made to *Section 7.2.1, Period 1- Visit 2 (Enrollment Visit, Day 0), Period 2- Visit 5 (Week 9), Period 3- Visit 8 (Week 18)*, second and third sentences to clarify that all grade 2 or higher AEs need to have resolved or stabilized prior to study product initiation.

At Visit 5 and Visit 8, prior to the initiation of study product, all AEs **grade 2 or higher judged to be related to study product** need to have resolved or stabilized. If the adverse event has not resolved within 7 days following Visit 2 ~~4~~ or 7, the PSRT ~~should~~**will** be consulted regarding progression into the next dosing period.

8. Edits to Table 7, *Mid-Period Visits*, Section 7.8, *Pharmacokinetics and Pharmacodynamics*, first paragraph, Table 10: *PK and PK Sample Collection* and Appendix III: *Sample Informed Consent Form* adds the collection of blood for PK to the Mid-Period Visits and corrects the anticipated maximum volume of blood required for PK.

Table 7: *Mid-Period Visits*

Period 1- Visit 3 (Week 4), Period 2- Visit 6 (Week 13), Period 3- Visit 9 (Week 22)		
Component		Procedures
Laboratory	Blood	• Blood for PK

Section 7.8, *Pharmacokinetics and Pharmacodynamics*

All participants will have blood (plasma and/or PMBCs) collected for PK. ~~It is anticipated that a maximum of 24 mL (3-8 mL CPTs) will be required for PK at each time point (all Mid-Period 1 (plasma only) and End-Period 2 End, and Period 3 End).~~ **(both plasma and PMBCs) visits. The blood volume drawn for PK will not exceed 34 mL at any visit.** In addition, rectal fluid will be collected via sponge for PK and PD. **See the sample collection schedule below.**

Table 10: *PK and PD Sample Collection Schedule*, blood row, mid-period collections added.

Blood (Plasma and PMBC)	Mid-Period 1 (Plasma only) Mid-Period 2 (Plasma only) Mid-Period 3 (Plasma only)
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Appendix I: *Schedule of Study Visits and Evaluations*, *Blood for PK* row modified:

LABORATORY										
BLOOD										
Blood for PK (PMBC and plasma)			X (Plasma only)	X		X (Plasma only)	X		X (Plasma only)	X

9. The following modifications have been made to Section 7.12, *Laboratory Evaluations* and Appendix 1, for purposes of consistency and proper use of the planned HSV testing.

Local Laboratory 2nd bullet, Rectal specimens, 2nd sub-bullet added:

- Rectal specimens
 - o **HSV 1/2 detection (if indicated)**

Local Laboratory 3rd bullet, Blood specimens, 7th and 8th sub-bullets modified:

- Blood specimens
 - o ~~HSV serology +/-~~
 - o ~~HSV 1/2 viral detection~~ **antibody**

Appendix 1: *Schedule of Study Visits and Evaluations* (Blood Section Row 9)

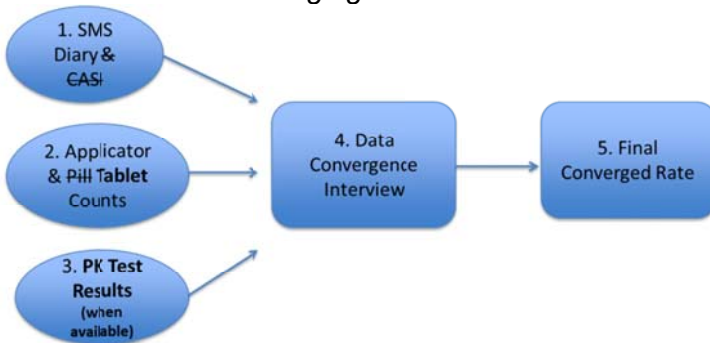
HSV 1/2 serology antibody	X									
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10. Section 7.13, *Specimen Collection and Processing*, has been corrected as the MTN Network Laboratory Manual no longer exists:

Each study site will adhere to the standards of good clinical laboratory practice, ~~the MTN Network Laboratory Manual~~ (<http://www.mtnstopshiv.org>), in accordance with current US Division of AIDS (DAIDS) Laboratory Requirements, MTN-017 Study-Specific Procedures Manual (<http://www.mtnstopshiv.org>), and site standard operating procedures for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory.

11. The following modifications have been made to Figure 3, *Method for Converging Adherence*, Section 7.10.2, *Adherence* and Appendix III: *Sample Informed Consent Form* to simplify the elements of the Product Adherence Counseling/Interview and text messages.

Figure 3: *Method for Converging Adherence*



Adapted from Pool R, Montgomery CM, Morar NS, et al. A mixed methods and triangulation model for increasing the accuracy of adherence and sexual behaviour data: The Microbicides Development Programme. *Plos One* 2010;5(7):e11800.

The following behavioral measures will be used to assess/enhance adherence:

As noted above, text from *Section 6.5* has been relocated to *Section 7.10.2, Adherence*, the new *Product Adherence Counseling/Interview* subsection has been inserted under the *Applicator and Pill Tablet-Counts* sub-section and the text has been simplified:

Product Adherence Counseling/ Interview

Study product adherence counseling will be provided to all study participants by site staff. Counseling will be provided in accordance with standard methods based on participant-centered strategies with discussions focused on describing experiences and identifying factors facilitating the ease/comfort of product use. Participants will also be counseled against product sharing and the impact that this could have on the outcome of the trial. Additional counseling regarding the issue of sharing will be provided if it is revealed. Towards the end of the discussion, counselors will help participants address what they can do or what can be done to increase ease/comfort/efficacy of product use.

Data Convergence Interview

~~Data on self-reports of product use, sexual behavior, and condom use sent through SMS and/or collected via CASI, and study product counts will be entered on a single data comparison form that will be made available to the site counselor. The Data Convergence Interview will be conducted at Mid-product use Period Visits and product use End Period Visits. when there are discrepancies between adherence data collected from the~~ **During the interview the site counselor will review with the participant his/her study product use, as reported via SMS report and/or CASI and the unused study product counts, and attempt to reconcile or explain any discrepancies to obtain their best estimate of product use. PK data collected during the daily TFV RG 1% gel or daily FTC/TDF 200mg/300mg tablet periods will also be reviewed with participants, when available.**

~~In such cases, the counselor will review the information with the participant to elicit information about possible discrepancies. The counselor's approach will be non-judgmental, reminding the participant that regardless of level of adherence, sexual behavior or condom use, they will not be disqualified from the study. These~~ **Adherence counseling and Data Convergence Interview sessions will be audio-recorded to ensure the quality and consistency of the counseling across all study sites, and to allow interview content to be analyzed for barriers and facilitators of product use as well as any reported discrepancies between SMS reports and unused study product counts. This analysis of data on the same topic emanating from different sources is generally referred to as research triangulation.³⁶ This process will allow for clarification of discrepancies between data sources and will be more informative than any single data source taken alone; all the independent data sources will be available to allow for analysis of different estimates of adherence.**

~~In the rare case in which a participant attends the visit, returns the applicators, but does not stay to speak with a counselor, we will analyze the available data from the SMS system and the returned applicators to determine the most likely adherence rate on a case-by-case basis.~~

Summary Database

The data comparison form together with the converged result of most likely adherence to product use will constitute the summary database on adherence, sexual behavior and condom use during the study.

Appendix 1: Schedule of Study Visits and Evaluations

BEHAVIORAL/COUNSELING										
Product use instructions and adherence counseling		X	X		X	X		X	X	
Data Convergence Interview	-	-	X	X	-	X	X	-	X	X
Product adherence counseling/interview		X	X	X	X	X	X	X	X	X

Appendix III, During the study, you will be asked to: repetitive language has been removed:

- Answer questions about your behavior, sexual behavior, sexual behavior practices related to your gel use, and your use of the study products. Some of these questions may be asked by computer and/or by daily text messages. The study staff will show you how to use the computer and how to send and receive text messages. This information is private and it will not be placed in your medical file.

Appendix III, edits to the You will be asked to use study product; as part of using study product you will: Section, fourth and fifth bullets edited, and a new sixth bullet was added:

- Answer a few short questions by cell phone via text messages that will ask about your use of the study product and sexual activity. [...]
- Review with the study staff your answers to the daily questions sent by text message, and the number of **unused** doses returned to the clinic, **and, when available, discuss the presence of study drugs in your blood**, so that you can help the study staff to understand when and how you used the study products. These conversations will be audio-recorded to ensure the session is done correctly at all sites.
- Answer questions on a computer about your behavior, including your sexual behavior, and your experiences using the study product and participating in the study. You will answer questions on a computer during each study period. **The study staff will show you how to use the computer.** This information is confidential and WILL NOT be placed in your medical record. The questionnaire will only be labeled with your study ID number.

Appendix III, the following text box has been inserted above the What do I do if I have questions? Section:

It is important that you take the study product(s) as instructed by study staff.

The amount of study drug in your blood will be checked routinely and the results will be discussed with you.

If you have any questions or concerns about taking the study product as directed, it is essential that you discuss your issue(s) with study staff now. After enrolling in the study, if you have any issue(s) with taking the study products, feel free to contact the clinic for guidance and/or tools that may help you.

12. To maintain consistency with Section 8.3.1, Adverse Events, Section 8.4.2, Reporting Requirements for this Study, edits have been modified to require study staff to document in CRFs all AEs reported by or observed in enrolled study participants regardless of severity and presumed relationship to study product will be collected and recorded on CRFs:

- Study staff will also report on CRFs the following subset of **all** AEs reported by or observed in enrolled participants:
 - All anorectal AEs Grade 1 and higher
 - All AEs of severity Grade 2 and higher

13. Section 13.6, Participant Confidentiality and Appendix III: Sample Informed Consent Form to highlight that Adherence Counseling Sessions and Data Convergence Interviews will be audio-recorded and content will be analyzed.

Section 13.6, Participant Confidentiality, the third full paragraph has been edited:

After receiving appropriate approval, all study documents/data will be properly disposed of, including the proper destruction and/or deletion of paper files, electronic study data, **and** electronic documents. Audio files of **In-depth Interviews** will be transcribed and immediately destroyed following a transcription quality assurance check. **Audio-recordings of Adherence Counseling Sessions and Data Convergence Interviews will be uploaded, ideally by the end of the day the interview takes place, to a secure site for review by the BRWG and deleted from the on-site audio recorder by site staff once receipt by the BRWG is confirmed. The recordings will be content analyzed for patterns of product use and destroyed following analysis, but no later than one year following the end of the study.** A member of the MTN Behavioral Research Working Group (BRWG) or designee is responsible for ensuring that these files have been destroyed.

Appendix III: *Sample Informed Consent Form*, first full paragraph after the *Other Possible Risks* section, new fifth sentence and modification to the sixth sentence:

[...] **These audio files will be reviewed and analyzed by another person who is outside of the research site and does not know you or have your personal information. The files will be destroyed after review and analysis.** In addition, if you agree and are selected to participate in the **in-depth** interviews, these will be audio recorded. [...]

Optional Study Activities Section, *Phone Interview*, initial/date text line has been modified:

<u>Phone Interview</u>	
_____	Yes, if chosen, I agree to participate in the audio-recorded phone interview
Initials & Date	
_____	No, I do not want to participate in the audio-recorded phone interview
Initials & Date	

14. To ensure participants are aware of the potential risks associated with sending and receiving text messages Appendix III: *Sample Informed Consent Form* has been updated.

What are the possible risks, side effects, and discomforts of this research study? Section, *Other Possible Risks* sub-Section, first full paragraph, new fourth and fifth sentence:

[...] You will be shown how to erase the text message sessions from your mobile phone by study staff. **However, as with all text messages sent from and received on your phone, it is possible that others may see your personal messages. Protections have been made to ensure that questions asked via text message are vague and will not directly convey information about your participation in this research study.** When staff talk with you about how and when you used the study products they will audio record the discussion using a digital audio recorder.[...]

15. For consistency with Section 7.10.2, *Adherence*, and Appendix III: *Sample Informed Consent Form* have been updated to reflect the possibility of a bonus for participants who respond to 85% or more of the text messages.

Section 7.10.2, *Adherence*, SMS Diary section, last sentence modified:

A bonus will also be given monthly to those who respond to ~~90~~**85%** of the daily messages.

Appendix III: edits to the, *Will there be any payments if I take part in this research study?*

[Site to insert information about local reimbursement:] [...] For **follow-up** phone calls ~~and/or text messages~~, you will receive [Site to insert amount \$xx]. **For text messages, you will receive up to [Site to insert amount \$xx]. [Sites to insert reimbursement for participants who reply to 85% or more of the daily text messages.]** For the in-depth phone interviews, you will receive [Site to insert amount \$xx].

16. The Tenofovir Gel Investigator's Brochure (IB) reference has been updated: CONRAD. Tenofovir Gel (GS-1278) Investigator's Brochure. ~~Fourth~~**Fifth** Edition, ~~November 12, 2010~~ **2 January 2013**.

The above information will be incorporated into the next version of the protocol at a later time if it is amended.