

LETTER OF AMENDMENT #01 TO:

MTN-014

**A Phase 1 Crossover Trial Evaluating the Pharmacokinetics of Tenofovir Reduced-Glycerin 1% Gel in the Rectal and Vaginal Compartments in Women**

**Version 2.0 dated May 1, 2013**

**DAIDS Protocol ID: 11885**

**IND #73,382**

**Date of Letter of Amendment: 29 August 2013**

---

*Site Instruction*

The following information impacts the MTN-014 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 includes a new exploratory study objective and the addition of a behavioral assessment to gain insight on participant's experience with directly observed dosing of tenofovir reduced-glycerin 1% gel in the rectal and vaginal compartments. In addition, the protocol now requires PT/INR testing at Screening for participants taking part in the Intensive Pharmacokinetics, Mucosal Gene Expression Microarray, Histology and Proteomics Subset, revises the Exclusion Criteria to restrict the enrollment of participants with a non-sexually transmitted RTI requiring treatment (i.e., symptomatic bacterial vaginosis or candidiasis) from enrolling in the study within 2 calendar months rather than 6 calendar months of treatment, adds an anorectal NAAT for GC/CT at Screening, modifies the number of rectal biopsies collected and clarifies inclusion criterion text. In addition, the visit window for the Product Administration Visit/Initiate Period 2 has been extended to allow for greater scheduling flexibility; resulting in revisions to the study duration, visit schedule, and study follow-up visit windows throughout the protocol. Finally, this LoA clarifies that in the event that more than 14 women are enrolled at the US site, only the first 14 participants (approximately) will be requested to provide vaginal and rectal tissue samples for the biopsy subset.

Text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

---

*Detailed Listing of Revisions*

- 1.) A new Exploratory Objective and Endpoint, have been added to the *Protocol Summary*, Section 3.3, *Exploratory Objectives*, Section 10.2.3, *Exploratory Study Endpoints*, and Section 13.6, *Participant Confidentiality* and various table and appendices within the protocol. In addition, a behavioral assessment has been added to the protocol at the Enrollment Visit and Period End Visits and to the informed consent:

*Protocol Summary*, a new exploratory objective and endpoint have been added:

Exploratory Objectives:

- 3. To evaluate the experience and acceptability of participation in a study requiring directly observed dosing (DOD) of tenofovir reduced-glycerin 1% gel vaginally and rectally and of daily clinic visits.**

Exploratory Endpoints:

- **Participant knowledge, attitudes and descriptions of their responses towards directly observed dosing of gel, and attending daily clinic visits.**

Section 3.3, *Exploratory Objectives*, new third objective:

3. **To evaluate the experience and acceptability of participation in a study requiring directly observed dosing (DOD) of tenofovir reduced-glycerin 1% gel vaginally and rectally and of daily clinic visits.**

Section 10.2.3, *Exploratory Study Endpoints*, new third bullet:

- **Participant knowledge, attitudes and descriptions of their responses towards directly observed dosing of gel, and attending daily clinic visits.**

Table 3: *Enrollment (Day 0)/ Study Product Administration Visit/ Initiate Period 1*, Table 5: *Visit 16: Period 1 End (Day 14)*:

Component	Procedures
Behavioral/Counseling	○ <b>Administer Behavioral Assessment</b>

**Note: The Behavioral Assessment may be audio recorded to ensure accurate transcription.**

Table 9: *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89\*)*

Component	Procedures
Behavioral/Counseling	○ <b>Administer Behavioral Assessment</b>

**Note: The Behavioral Assessment may be audio recorded to ensure accurate transcription.**

Section 13.6, *Participant Confidentiality*, new third paragraph:

**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-recordings of the Behavioral Assessment will be transferred to the appropriate study form and transcribed and/or chart noted, as needed. Ideally the audio recording is destroyed as soon as the study form has been filled out and transcription/chart noting has occurred. Study staff is responsible for ensuring that these files have been destroyed.**

Appendix I: *Schedule of Study Visits and Evaluations* and note added:

	Visit 1 SCR	Visit 2 ENR Study Product Admin. Visit/ Initiate Period 1 (Day 0)	Visits 3-15, Study Product Admin Visits	Visit 16 /Period 1 End. (Day 14)	Safety Phone Call	Visit 17 Washout Visit (Day 35)	Visit 18 Study Product Admin Visit/ Initiate Period 2 (Day 56- 75)*	Visits 19-31 Study Product Admin Visits	Visit 32 Period 2 End/ Final Clinic (Day 70- 89)*	Safety Phone Call/ Terminati on (Day 77- 96)*
<b>BEHAVIORAL/COUNSELING</b>										
<b>Administer DOD Experience Assessment CRF</b>		<b>X</b>		<b>X</b>					<b>X</b>	

**Note: Administration of the Behavioral Assessment may be audio recorded to ensure accurate transcription.**

Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*: *At your Enrollment Visit, you will have the following study procedures* Section, new sixth bullet:

- **Be asked to answer a few short questions about your study participation expectations. To ensure that we are accurately capturing your comments when administering this questionnaire, this conversation may be recorded. The audio files will be put into writing by the person interviewing you or by another person who does not know you and does not have your personal information. The audio recordings will be destroyed as soon as they have been put into writing. The person in charge at this site will make sure that these recordings have been destroyed.**

Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*: *Other Procedures*: Section, new third bullet:

- **At the Period End Visits you will be asked to answer a few short questions about your experience while taking part in this study. Some of these questions relate to your experience using the gel while being observed by study staff. Your answers will be kept confidential. To ensure that we are**

accurately capturing your comments when administering this form, this conversation may be recorded. As previously mentioned, these audio recordings will be destroyed.

- 2.) Prothrombin time (PT)/International normalized ratio (INR) will be required at Screening in Section 5.3, *Exclusion Criteria*, Table 2: *Screening Visit*, Section 7.16, *Laboratory Evaluations*, Appendix I: *Schedule of Study Visits and Evaluations* and Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*.

Section 5.3, *Exclusion Criteria*:

- 2) Laboratory abnormalities at Screening greater than or equal to a Grade 2\*, **unless otherwise stated**:

**e.) Biopsy Subset Only: Prothrombin time (PT) > 1.25 × the site laboratory ULN / International normalized ratio (INR) > 1.5 × the site laboratory ULN**

Table 2: *Screening Visit*:

Screening Visit		
Component		Procedures
Laboratory	Blood	<ul style="list-style-type: none"> <li>● Collect blood for: [...]</li> <li>○ <b>PT/INR*</b></li> </ul>

Section 7.16, *Laboratory Evaluations*:

Local Laboratory

- **PT/INR**

Appendix I: *Schedule of Study Visits and Evaluations*:

	Visit 1	Visit 2	Visits 3-15	Visit 16	Safety Phone Call	Visit 17	Visit 18	Visits 19-31	Visit 32	Safety Phone Call/Termination
PT/INR	∞									

Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*, subsection, *Tissue Samples, [Sites participating in the Rectal and Vaginal Tissue Subset]*.

Study clinicians [...], each about the size of a grain of rice. **We will first test the ability of a small amount of your blood [xx mL] to clot properly and these results will help us know whether it is safe to take these tissue samples.**

- 3.) Section 5.3, *Exclusion Criteria*, is modified to exclude participants with an RTI requiring treatment within 2 calendar months rather than 6 calendar months prior to Enrollment.

- 1) Participant report of any of the following:

[...]

- f) ~~STI or reproductive tract infection (RTI)~~ requiring treatment in the 6 calendar months prior to Enrollment

[...]

- o) Other reproductive tract infection (RTI) (i.e., symptomatic BV and candida) requiring treatment in the 2 calendar months prior to Enrollment**

- 4.) The inclusion of a rectal swab for NAAT for GC/CT has been added to Table 2: *Screening Visit*, Section 7.16, *Laboratory Evaluations*, and Appendix I: *Schedule of Study Visits and Evaluations* and Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*.

Table 2: *Screening Visit*:

Screening Visit		
Component		Procedures
Laboratory	Rectal Samples	<ul style="list-style-type: none"> <li>● <b>Rectal GC/CT by NAAT</b></li> </ul>

Section 7.16, *Laboratory Evaluations*:

Local Laboratory

- **Rectal GC/CT by NAAT**

Appendix I: *Schedule of Study Visits and Evaluations:*

	Visit 1 SCR	Visit 2 ENR	Visits 3-15	Visit 16	Safety Phone Call	Visit 17	Visit 18	Visits 19-31	Visit 32 Period 2	Safety Phone Call/ Termin ation
LABORATORY (vaginal and , cervical, and rectal swabs as required)										
Rectal GC/CT by NAAT	X									

Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*, What procedures will be performed for research purposes, Screening Procedures Section, fourth bullet modified:

- Perform a rectal exam. The study doctor or nurse will look at the outside of your anus and the area around your anus. He/she will then insert a lubricated gloved finger, into the anal canal to check for any ~~issues~~problems. **They will also take some fluid to test for sexually transmitted infections or diseases (commonly known as STIs or STDs). The clinician and/or designee will first insert a short hollow tube called an anoscope inside your rectum and then insert a swab or sponge through the anoscope to collect the fluid.**

- 5.) The number of rectal biopsies has been modified within Section 2.8, *Other Protocol Considerations*, subsection *Justification for the use of a Flexible Sigmoidoscope to Collect Rectal Biopsies in a Subset of Participants*, Tables 2, 5, 9, Section 7.10.3, *Participants Who Permanently Discontinue for Other Reasons*, Section 7.11, *Participants Who Temporarily Hold Study Product*, Table 12, *Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset Sample Collection*, Section 7.14, *Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset*, Section 7.16, *Laboratory Evaluations*, Appendix I: *Schedule of Study Visits and Evaluations*, Appendix III: *Sample Informed Consent Form (Screening, Enrollment Long-Term Storage)*.

Section 2.8, *Other Protocol Considerations*, subsection *Justification for the use of a Flexible Sigmoidoscope to Collect Rectal Biopsies in a Subset of Participants*:

Rectal biopsies will be collected in a subset of participants using a flexible sigmoidoscope. A flexible sigmoidoscope allows for the collection of a sufficient number of rectal biopsies (~~6~~) at the preferred distance from the anal verge (~15-20 cm). [...]

Table 2: *Screening Visit*

Laboratory	Rectal Samples	
		• Collect rectal biopsies for mucosal gene expression microarray, <b>histology and proteomics</b>

Table 5: *Visit 16: Period 1 End (Day 14)*, and Table 9, *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89\*)* Laboratory row, Rectal samples row has been updated:

Laboratory	Rectal Samples	
		• Rectal biopsies for PK, and mucosal gene expression microarray, <b>histology and proteomics</b>

Section 7.10.3, *Participants Who Permanently Discontinue for Other Reasons* and Section 7.11, *Participants Who Temporarily Hold Study Product*:

- PK/PD/mucosal gene expression microarray, **histology and proteomics** specimen collection

Table 12 *Intensive Pharmacokinetics, and Mucosal Gene Expression Microarray, Histology and Proteomics Subset Sample Collection*:

Visit	Specimens Collected for PK	Specimens Collected for Microarray	Specimens Collected for Histology	Specimens Collected for Proteomics
Visit 1: Screening		<ul style="list-style-type: none"> <li>• 1 Vaginal Biopsy <sup>■</sup></li> <li>• 4 2 Rectal Biopsies <sup>■</sup></li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>
Visit 16: Period 1 End	<ul style="list-style-type: none"> <li>• 2 Vaginal Biopsies</li> <li>• 4 Rectal Biopsies</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Vaginal Biopsy</li> <li>• 2 Rectal Biopsies</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>

Visit	Specimens Collected for PK	Specimens Collected for Microarray	Specimens Collected for Histology	Specimens Collected for Proteomics
Visit 32: Period 2 End	<ul style="list-style-type: none"> <li>• 2 Vaginal Biopsies</li> <li>• 4 Rectal Biopsies</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Vaginal Biopsy</li> <li>• 2 Rectal Biopsies</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>	<ul style="list-style-type: none"> <li>• 1 Rectal Biopsy</li> </ul>

Section 7.14, *Intensive Pharmacokinetics, and Mucosal Gene Expression Microarray, Histology and Proteomics Subset*, first paragraph, last sentence:

Details regarding the quantity and timing of mucosal sample collection for intensive PK, and mucosal gene expression microarray, **histology and proteomics** for this subset are described in Table 12.

Section 7.16, *Laboratory Evaluations, Network Laboratory* Subheading, seventh bullet has been modified:

- Mucosal gene expression microarray, **histology and proteomics**

Appendix I: *Schedule of Study Visits and Evaluations*:

	Visit 1 SCR	Visit 2 ENR	Visits 3-15	Visit 16	Safety Phone Call	Visit 17	Visit 18	Visits 19-31	Visit 32 Period 2	Safety Phone Call/Termination
Rectal biopsies for PK, and gene expression microarray, <b>histology and proteomics</b>	∞			■					■	

Appendix III: *Sample Informed Consent Form (Screening, Enrollment Long-Term Storage)*, subsection, *Tissue Samples, Sites participating in the Rectal and Vaginal Tissue Subset please insert the following language* subsection, first sentence of the second paragraph:

Study clinicians will take approximately 1 small tissue sample from the vagina and ~~4~~ **44** small tissue samples from your rectum at your visit today, each about the size of a grain of rice.

Within the same section, the table has been modified:

Visit	Number of biopsies collected	
	Vaginal	Rectal
Screening	1	<del>1</del> <b>44</b>
Visit 16: Period 1 End Visit (Day 14)	3	<del>6</del> <b>68</b>
Visit 32: Period 2 End Visit (Day 70-89)	3	<del>6</del> <b>68</b>
Total	7	<del>13</del> <b>1320</b>

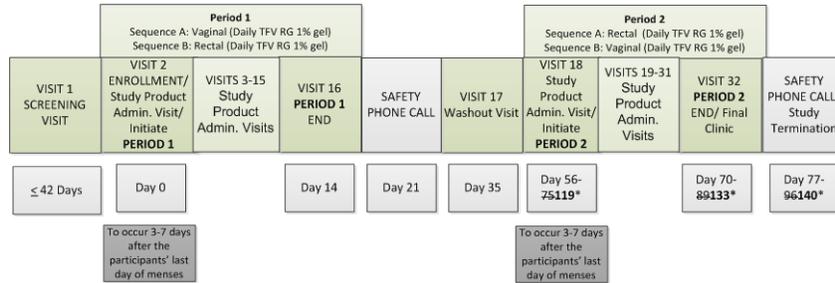
6.) Section 5.2, *Inclusion Criteria*, number 16 has been clarified:

16) Willing to ~~refrain~~ **abstain from** the use of non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and/or other drugs that are associated with the increased likelihood of bleeding following mucosal biopsy collection for 72 hours prior to and following the collection biopsies

7.) The visit windows for the Product Administration Visit/Initiate Period were increased and subsequent follow-up visit windows were adjusted to allow for greater scheduling flexibility. Modifications were included within the *Study Duration* section of the *Protocol Summary*, Figures 1 and 2, *Study Visit Schedule*, Section 4.6, *Sequence and Duration of Participation*, Table 7 in Section 7.6, *Visit 18 Study Product Administration/Initiate Period 2 (Day 56-75)*, Table 9 in Section 7.8, *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89\*)*, Appendix I: *SCHEDULE OF STUDY VISITS AND EVALUATIONS*, and Appendix III: *SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, LONG-TERM STORAGE)*

Study Duration: Accrual will require approximately 10 months per site. Each enrolled participant will be followed for approximately 10-~~13~~ **1320** weeks, depending upon their menses schedule.

Study Visit Schedule:



\* Visit schedule will vary based upon participants' menses.

Section 4.6, *Sequence and Duration of Participation:*

The total duration of participation from the Enrollment Visit to Termination is anticipated to be 10-4320 weeks, depending upon participants' menses schedule [...].

Section 7.6, *Visit 18: Study Product Administration/Initiate Period 2 (Day 56-75/119\*)*

Table 7: Visit 18 Study Product Administration/Initiate Period 2 (Day 56-75/119\*)

Visit 18: Study Product Administration/Initiate Period 2 (Day 56-75/119*)
---

Section 7.8, *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89/133\*)*

Table 9: Visit 32: Period 2 End/Final Clinic Visit (Day 70-89/133\*)

Visit 32: Period 2 End/Final Clinic Visit (Day 70-89/133*)
--

APPENDIX I: *Schedule of Study Visits and Evaluations*, Visit Description Row, Visits 18, 32 and Safety Phone call:

Visit 18 Study Product Admin Visit/ Initiate Period 2 (Day 56-75/119)*	Visit 32 Period 2 End/ Final Clinic (Day 70-89/133)*	Safety Phone Call/ Termination (Day 77-96/140)*
--	--	---

APPENDIX III: *Sample Informed Consent Form (Screening, Enrollment Long-Term Storage), Enrollment and Follow-up Procedures* section, third paragraph:

You will be in the study for approximately 10-4320 weeks, depending upon the timing of your menstrual cycle and when you are able to schedule your visits, from the time you enter the study up until your follow-up phone call at the end of the study. [...]

- 8.) In the event that more than 14 women are enrolled at the US site, only the first 14 participants (approximately) will be requested to provide vaginal and rectal tissue samples for the Intensive Pharmacokinetics, Mucosal Gene Expression Microarray, Histology and Proteomics Subset, thus throughout the protocol the note attached to the primary endpoint has been modified, Table 2: *Screening Visit*, Table 5: *Visit 16: Period 1 End (Day 14)*, Table 9: *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89\*)*, Section 7.14, *Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset* and Table 12: *Intensive Pharmacokinetics and Mucosal Gene Expression Microarray Subset Sample Collection*, Section 10.6.1, *Primary Data Analyses on PK Measures*, Appendix I: *Schedule of Study Visits and Evaluations* and Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*:

Throughout the protocol the note attached to the Primary Endpoint has been modified:

*Note: All US participants (a* ~~Approximately 14 total~~ *participants* **at the US site only will supply vaginal and rectal tissue samples. See Section 7.14 for additional details.**

Table 2: *Screening Visit*:

■ To be collected/performed during the screening process at the US site on ~~all~~ women **providing vaginal and rectal tissue samples** who have not already had their screening terminated due to ineligibility (~~samples to be collected are for gene expression only~~).

Table 5: *Visit 16: Period 1 End (Day 14)* and Table 9: *Visit 32: Period 2 End/Final Clinic Visit (Day 70-89\*)*:

\* If indicated, ■ All ~~p~~Participants at the US site ~~only~~ **providing vaginal and rectal tissue samples**. See Section 7.14 for additional details.

Section 7.14, *Intensive Pharmacokinetics, and Mucosal Gene Expression Microarray, **Histology and Proteomics** Subset*:

~~Approximately 14 p~~Participants at ~~a single~~the US site must agree to the collection of biopsies in order to take part in MTN-014. ~~All~~**Approximately 14** women at the US site, provided that they are not found to be ineligible for other reasons, will provide ~~a~~ vaginal and rectal ~~biopsy~~ **biopsies**. ~~It is anticipated that all US participants (approximately 14 participants) will be enrolled into the study and take part in the biopsy subset. [...]~~

Table 12: *Intensive Pharmacokinetics, and Mucosal Gene Expression Microarray, **Histology and Proteomics** Subset Sample Collection*:

■ To be collected/performed during the screening process at the US site on all women **providing vaginal and rectal tissue samples** who have not already had their screening terminated due to ineligibility

Section 10.6.1, *Primary Data Analyses on PK Measures*, sixth sentence:

For the tissue concentrations collected in **approximately** 14 participants in the US site, a signed rank Wilcoxon test will be also conducted.

Appendix I: *Schedule of Study Visits and Evaluations*:

\*= If indicated ∞=To be collected at the US site on ~~all~~women **providing vaginal and rectal tissue samples** who have not already had their screening terminated due to ineligibility (~~samples to be collected for gene expression only~~), ■= To be collected on a subset of approximately 14 ~~US~~participants, ~=Sites to reference SOPs regarding participant reimbursement, ◇= PD and biomarkers only, ▲= to be performed at the final study product administration visit

Appendix III: *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage)*, subsection, *Tissue Samples, first paragraph*:

Approximately 14 participants from the United States [~~Site participating in the Rectal and Vaginal Tissue Subset to insert the following language:~~, all of the participants at this site,] will provide rectal and vaginal tissue (biopsies) to help researchers better understand the how the study drug enters and exits the body and what effect the drug has on the tissue, including what effect the study drug has on your genes.

Appendix III: *SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, LONG-TERM STORAGE)*, subsection, *Tissue Samples, [Site participating in the Rectal and Vaginal Tissue Subset text box*:

**It is important that you know that approximately 14 females from this site will be selected to take part in the Rectal and Vaginal Tissue procedures; study staff will tell you more about the procedures.** If you agree to take part in this study **and to provide vaginal and rectal tissue samples**, you will have an exam of your vagina using a speculum and an exam of your rectum using flexible sigmoidoscopy.

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