LETTER OF AMENDMENT #01 TO:

MTN-007
DAIDS DOCUMENT ID: 10736

A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and Acceptability Study of Tenofovir 1% Gel

Version 1.0 / 8 April 2009

CONRAD IND #: 73,382

Letter of Amendment Date: 16 September 2009

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-007 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. IRB/EC approval is required before implementation of the revisions contained in this LoA.

The following information will also impact the sample informed consent. Site IRBs/ECs are responsible for assessing whether and how the changes included in this LoA are to be communicated to study participants. All IRB/EC requirements must be followed.

Please file this LoA and all associated IRB/EC correspondence in your essential documents files for MTN-007.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-007. This LoA provides clarification on the following items:

1. Modifications to Section 8 to update communication pattern regarding adverse event reporting. These changes do not impact the degree or details of safety reporting in MTN-007
2. Clarifications to Study Product section
3. Correction of study duration throughout the protocol
4. Modification to reflect that history of reproductive and urinary tract infections will also be collected by participant report
5. Elimination of vaginal pH from Screening Visit
6. Modifications to reflect that urine GC/CT will be performed as clinically indicated
7. Elimination of references to INR and PTT in Section 5.3, Exclusion Criteria, as they are not included in the Screening Procedures
8. Clarification regarding grading scale for glycosuria
9. Other minor corrections and updates

Implementation

This LoA is official MTN-007 protocol documentation. Prior to implementing the revisions listed below, the MTN-007 study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. CONRAD will submit this LoA to the United States Food and Drug Administration (FDA) for inclusion in Investigational New Drug (IND) application #73,382. Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

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

Detailed Listing of Revisions

1. **The following changes are made to Section 8, Assessment of Safety to reflect the guidelines put forth in the MTN-007 Clinical Trials Agreement:**

Section 8.4, Expedited Adverse Event (EAE) Reporting Requirements, Expedited Adverse Event Reporting subsection, first paragraph, first sentence:

The adverse events that must be reported in an expedited fashion **to the DAIDS Regulatory Compliance Center (RCC) Safety Office via DAIDS Adverse Events Reporting System (DAERS)** include all serious adverse events (SAEs) as defined by May 1996 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice: Consolidated Guidance (E6) regardless of relationship to the study agent(s).

Section 8.4, Expedited Adverse Event (EAE) Reporting Requirements, Expedited Adverse Event Reporting subsection, second, third, and fourth paragraphs:

All sites will report all EAEs expeditiously to RCC via the electronic reporting system DAERS established by DAIDS. The RCC Safety Office will also prepare the draft safety reports and send them to the CONRAD and DAIDS MOs for review.

Study sites will be contacted by the DAIDS MO if any further information or clarification is needed after the report is evaluated by CONRAD and DAIDS MOs. The RCC Safety Office will then prepare the final report which will go to CONRAD for signature and submission to the FDA. Copies of this final report will be filed with CONRAD and RCC. Additionally, the RCC Safety Office will distribute safety reports to all DAIDS sites that use products under investigation in this study.

For all EAEs submitted, sites must file an ~~initial report and an~~ **RCC** update ~~to CONRAD and the DAIDS Medical Officer~~ with the final or stable outcome unless the initial EAE submitted had a final or stable outcome noted already.

Section 8.4, Expedited Adverse Event (EAE) Reporting Requirements, EAE Reporting Requirements for this Study, subsection:

~~Any adverse event that is determined to be serious (whether expected or unexpected) regardless of relationship to the study agent(s) must be immediately reported to CONRAD and the DAIDS Medical Officer (21 CFR 312.64). An EAE Form must be completed and sent to CONRAD and the DAIDS Medical Officer within 3 business days (by 5 PM Eastern Time (ET)) after site awareness that the event has occurred at a reportable level. DAIDS MO will review and discuss the EAE report with CONRAD to address any concerns.~~

~~CONRAD will notify the FDA of any unexpected serious adverse events associated with the use of the drug as soon as possible, but no later than 7 calendar days after initial receipt of the information from the investigator.~~

~~For unexpected serious adverse events associated with the use of the drug, CONRAD will submit the safety reports provided by the sites to the IND no later than 15 calendar days after the initial receipt of the information and send copies of the submission to the DAIDS MO and the Regulatory Compliance Center (RCC) (to be placed in the DAIDS IND file for tenofovir).~~

Sites using the DAERS internet-based reporting system for submission of EAEs to DAIDS will follow the DAERS processes as outlined in the DAERS training information. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov or from within the DAERS application itself.

If the site cannot use DAERS to report an AE on an expedited basis, the AE must be documented on the DAIDS Expedited Adverse Event Reporting Form (EAE Reporting Form) available on the RCC website: http://rcc.tech-res.com (and MOP, if applicable), and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please contact the RCC. DAIDS EAE forms should be submitted to DAIDS through the Regulatory Compliance Center (RCC) Safety Office via email (rccsafetyoffice@tech-res.com) or by calling 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.]

Section 8.5, Pregnancy and Pregnancy Outcomes, third paragraph, last sentence:

The SDMC will prepare **and provide to CONRAD** a quarterly report on all pregnancies and their outcomes ~~(if there are any)~~**. The SDMC will also prepare an annual summary report of all AEs for the annual IND reports (submitted by CONRAD).**

2. **The following updates are made to the second and third paragraphs in Section 6.2, Administration:**

Second paragraph:

~~Based on randomization number, each participant will be assigned a carton of applicators. From this assigned carton the participant will receive one applicator for administration~~ a**A**t the Treatment 1 Visit~~.~~**, participants will receive one applicator of their assigned study product for administration under observation**~~. At this visit, the participant's first dose (the entire contents of one applicator) of study product will be administered by the Investigator of Record (IoR) or designee.~~

Third paragraph, first and second sentences:

At the Treatment 2 Visit the participants will receive ~~their assigned carton with the remaining~~ **8** applicators **of their assigned gel for the 7-day administration period**. **Participants are provided one extra applicator should an applicator not be usable for any reason.**

3. **The study duration has been modified throughout the protocol to accurately reflect the visit windows outlined in Section 7 of the protocol.**

Protocol Summary:

Study Duration: Participant accrual will take approximately 5 months and each participant

will be on study for approximately 4 to ~~8~~ **11** weeks. The total duration of the study will be approximately ~~7~~ **8** months.

Section 4.6, Expected Duration of Participation:

Each participant will be on study for approximately 4 to ~~8~~ **11** weeks. The total duration of the study will be approximately ~~7~~ **8** months.

Appendix VII: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study? section, third paragraph, first sentence:

You will be in the study for about 4 to ~~8~~ **11** weeks from the time of your Enrollment Visit (today) up until your follow-up phone call at the end of the study, and will use the study gel for a total of 8 days.

4. **Section 5.3, Exclusion Criteria, item 2, first sentence is clarified to reflect that history of reproductive or urinary tract infections will be collected by participant report and the last sentence is clarified to reflect inclusion of HSV-1 positive individuals with no active lesions:**

First sentence:

At screening~~,~~**: history, reported symptoms, and/or** clinical or laboratory diagnosis of active rectal or reproductive tract infection requiring treatment per current CDC guidelines or urinary tract infection (UTI).

Last sentence:

Note that an **HSV-1 or** HSV-2 seropositive diagnosis with no active lesions is allowed, since treatment is not required

5. **Section 7.1, Screening Visit and Appendix I have been updated to eliminate collection of vaginal pH at the Screening Visit. The Sample Informed Consent document (Screening) has been updated accordingly.**

Section 7.1, Screening Visit, Table 8: Screening Visit:

~~Vaginal Specimens~~	~~• Vaginal pH~~

Appendix I: Schedule of Study Visits and Evaluations:

~~Vaginal pH~~	~~X~~								

Appendix VI: Sample Informed Consent Document (Screening), What Do I Have To Do If I Take Part In The Screening Exams And Tests? section:

- ~~Have a sample of fluid taken from your vagina, if you are a woman~~

6. **Sections 7.2, 7.3, 7.5, 7.6, 7.8.4, 7.9, and Appendix I have been updated to reflect that urine GC/CT will be performed as indicated at all visits except for the Screening Visit. Section 7.9 has also been updated to reflect that Rectal GC/CT will be performed at the Interim Visit as indicated. The Sample Informed Consent document (Enrollment) has been updated accordingly:**

Section 7.2, Enrollment Visit, Table 9: Enrollment/Baseline Evaluation Visit:

Urine	• Collect urine sample o ♀ Qualitative hCG o **GC/CT***

Section 7.3, Treatment 1 Visit, Table 10: Treatment 1 Visit:

Urine	• Collect urine sample o ♀ Qualitative hCG o **GC/CT***

Section 7.5, Treatment 2 Visit, Table 12: Treatment 2 Visit:

Urine	• Collect urine sample o ♀ Qualitative hCG o **GC/CT***

Section 7.6, Final Clinic Visit, Table 13: Final Clinic Visit:

Urine	• Collect urine sample o ♀ Qualitative hCG o Dipstick urinalysis U/A o **GC/CT***

Section 7.8.4, Participants Who Are Discontinued from Study Product by the Site Investigator, Table 15: Early Termination Visit:

Urine	• Collect urine sample o ♀Qualitative hCG o Dipstick U/A o **GC/CT***

Rectal Specimens	• **Anorectal swabs** o ***Rectal *Chlamydia trachomatis* and *Neisseria gonorrhea* by NAAT**

Section 7.9, Interim Contacts and Visits, Table 16: Interim Contacts and Visits:

Urine	• Collect urine sample* o ♀ Qualitative hCG o Dipstick urinalysis U/A o **GC/CT**

Rectal Specimens	• **Anorectal swabs** ***Rectal *Chlamydia trachomatis* and *Neisseria gonorrhea* by NAAT**

Appendix I: Schedule of Study Visits and Evaluations:

Urine GC/CT by NAAT	X	▲	▲		▲	▲		▲	▲

Rectal GC/CT by NAAT	X				▲	▲		▲	▲

Appendix VII: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study? section, At most visits, we will ask you to do the following subsection:

- **Have your urine tested for gonorrhea and chlamydia if the study doctor thinks you need to be tested**

Appendix VII: Sample Informed Consent Document (Enrollment), addendum to Appendix VII: MTN-007: Schedule of Study Visits and Evaluations for Participants:

Gonorrhea and chlamydia tests	**X**	▲	▲		▲	▲		▲

7. **In Section 5.3, *Exclusion Criteria*, item 4j is modified. This statement is removed as these labs are not being performed at the Screening Visit:**

   j. History of bleeding problems ~~(i.e. INR > 1.5× the site laboratory ULN or PTT > 1.25× the site laboratory ULN)~~

8. **In Section 8.3.1, *Adverse Events*, the grading for glycosuria is clarified in the third paragraph, last sentence:**

Please note that the grading scale for proteinuria should also be used for grading glycosuria.

9. **The following minor corrections and clarifications are made to the protocol:**

Protocol Team Roster:

Yevgeny Grigoriev, MD, PhD
SDMC Clinical Affairs Safety Associate
Clinical Affairs, SCHARP
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North
LE-400, PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-3440
Fax: 206-667-4812
Email: ygrigori@scharp.org

Laura McKinstry, MPH
SDMC Project Manager
SCHARP-FHCRC
1100 Fairview Avenue North
PO Box 19024
LE-400, PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7322
Fax: 206-667-4812
Email: lamckins@scharp.org

Marla Husnik, MS
SDMC Statistical Research Associate
SCHARP-FHCRC
1100 Fairview Avenue North
PO Box 19024
M2-C200, PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-5633
Fax: 206-667-4812
Email: marla@scharp.org

References to applicator codes have been removed from Sections 6.5 and 7.12 as the participants will not receive the applicator codes:

Section 6.5, Assessment of Participant Adherence, fifth sentence:

To access the PRS, participants call a toll-free number, identify themselves to the system using a unique ID number (corresponding to the participant identification number (PTID)), and then respond to pre-recorded questions on product use~~, the code number of the applicator used,~~ and whether there is any comment related to this particular occasion of product use.

Section 7.12, Behavioral Measures, Adherence Questionnaire subsection, second sentence:

Responses to specific questions on product use since the prior call (e.g., "Did you use the product? Y/N~~; Enter applicator number~~) will constitute a measure of adherence.

Section 7.1, Screening Visit, Table 8: Screening Visit, reference to urinalysis is corrected to reflect inclusion of testing for nitrites, not nitrates:

Urine	• Collect urine sample o ♀ Qualitative hCG o Dipstick urinalysis (UA) for protein, glucose, nitr~~a~~ites, and leukocyte esterase o *Chlamydia trachomatis* and *Neisseria gonorrhea* by nucleic acid amplification testing (NAAT)

Informed consent for the Storage and Future Testing of Specimens is added to the Enrollment Visit:

Section 7.2, Enrollment Visit, Table 9: Enrollment/Baseline Evaluation Visit (Day 0, Within 36 Days of Screening Visit:

Administrative	• Obtain written informed consent for Enrollment **and Storage and Future Testing of Specimens** • Review/update demographic information • Review/update locator information • Provide test results • Eligibility assessment • Randomization • Provide reimbursement for study visit • Schedule next study visit

Appendix VII: Sample Informed Consent Document (Enrollment), What Do I Have To Do If I Am In This Study?, section, second paragraph, second bullet:

- **Be asked to complete the informed consent document for the storage and future testing of specimens. You will only be asked to sign a separate consent document if you give your permission for the study staff to store your specimens for future testing**

HSV Serology is omitted from Section 7.2, Enrollment Visit to maintain consistency with Appendix VII: Sample Informed Consent document (Enrollment). Appendix I has been modified accordingly:

Section 7.2, Enrollment Visit, Table 9: Enrollment/Baseline Evaluation Visit (Day 0, Within 36 Days of Screening Visit:

Blood	• Collect blood specimens ~~o HSV serology~~ o *Syphilis RPR (confirmatory tests as needed) o *HIV-1 serology (confirmatory tests as needed) o Plasma archive

Appendix I: Schedule of Study Visits and Evaluations:

HSV serology	X	~~X~~							

Section 7.13.1, Local Laboratory Testing, has been updated to clarify that Rectal GC/CT by NAAT (SDA) will be performed at the local laboratory level instead of at the MTN Network Laboratory:

o **Rectal GC/CT by NAAT**

Section 7.13.2 Network Laboratory Testing has been updated to remove references to rectal GC/CT by NAAT (SDA) and urine GC/CT by NAAT as these tests will be performed at the local laboratory level:

Rectal Specimens: ~~all specimens will be collected and stored locally for analysis by the MTN Network Laboratory.~~

- Rectal swabs
    - Microflora
    - ~~GC/CT by NAAT (SDA)~~

~~Urine Specimens:~~

- ~~GC/CT by NAAT~~

Sections 7.2, 7.3, 7.5, 7.6 and Appendix I have been modified to reflect that demographic information will only be collected at the Screening Visit:

Appendix I: Schedule of Study Visits and Evaluations has been re-formatted to ensure that all columns appear on a single page. Please note that the changes to Appendix I as indicated throughout this LoA also included in the revised version of Appendix I. The original and revised versions of Appendix I are included on the following pages.

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

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS *(original)*

	SCR	ENR	TRTMT 1	F/U PHONE CALL	TRTMT 2	FINAL	F/U PHONE CALL	EARLY TERM.	INTERIM
Informed consent	X	X							
PTID	X								
Demographics	X	X	X		X	X		X	X
Locator information	X	X	X		X	X		X	X
Test results		X	▲		▲	▲		▲	▲
Eligibility assessment	X	X							
Randomization		X							
Reimbursement	X	X	X		X	X		X	
Schedule next study visit	▲	X	X		X				▲
Schedule follow-up phone call			X			X		X	
Medical history	X	X	X		X	X		X	X
Menstrual history	♀	♀	♀		♀	♀		♀	♀
Concomitant meds	X	X	X		X	X		X	X
Physical exam	X	X	X		▲	X		▲	▲
Rectal exam	X	X	X		▲	X		▲	▲
Document pre-existing conditions		X							
HIV pre-and-post test couns	X	▲				X		X	▲
HIV/STI risk reduction couns	X	X	X		X	X		X	X
Contraceptive couns	X	X	X		X				
Adherence couns (protocol and/or product use)		X	X		X				
AE assessment			X	X	X	X	X	X	▲
Condoms	X	X	X		X	X		X	X
Baseline behavioral quest.		X							
Phone reporting system					X				
Product acceptability quest.*						X		X	
Qualitative hCG	♀	♀	♀		♀	♀		♀	♀
Dipstick UA	X					X		X	▲
CBC	X					X		X	▲
BUN, creatinine, ALT, AST	X					X		X	▲
Syphilis RPR	X	▲				X		X	▲
Confirm syphilis	▲	▲				▲		▲	▲
HIV-1 serology	X	▲				X		X	▲
Confirm. HIV-1	▲	▲				▲		▲	▲
Plasma archive		X							
HBsAG	X								
HSV serology	X	X							
Urine GC/CT by NAAT	X							▲	
~~Vaginal pH~~	~~X~~								
Rectal GC/CT by NAAT	X	▲	▲		▲	▲		▲	▲
Rectal microflora		X	X			X			
Rectal cytokines		X	X			X			
Normosol-R enema		X	X			X			
Rectal lavage,effluent, sloughing		X	X			X			
Fecal calprotectin		X	X			X			
Anoscopy and biopsies		X	X		▲	X			
Flex. sigmoidoscopy and biopsies		X	X			X			
Study product*			X		X				
Collect used & unused product*						X		X	▲

▲ If indicated ♀ for females of childbearing potential *for participants in treatment arms

APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS *(Revised)*

	SCR	ENR	TRTMT 1	F/U PHONE CALL	TRTMT 2	FINAL	F/U PHONE CALL	EARLY TERM.	INTERIM
Informed consent	X	X							
PTID	X								
Demographics	X								
Locator information	X	X	X		X	X		X	X
Test results		X	▲		▲	▲		▲	▲
Eligibility assessment	X	X							
Randomization		X							
Reimbursement	X	X	X		X	X		X	
Schedule next study visit	▲	X	X		X				▲
Schedule follow-up phone call			X			X		X	
Medical history	X	X	X		X	X		X	X
Menstrual history	♀	♀	♀		♀	♀		♀	♀
Concomitant meds	X	X	X		X	X		X	X
Physical exam	X	X	X		▲	X		▲	▲
Rectal exam	X	X	X		▲	X		▲	▲
Document pre-existing conditions		X							
HIV pre-and-post test couns	X	▲				X		X	▲
HIV/STI risk reduction couns	X	X	X		X	X		X	X
Contraceptive couns	X	X	X		X				
Adherence couns (protocol and/or product use)		X	X		X				
AE assessment			X	X	X	X	X	X	▲
Condoms	X	X	X		X	X		X	X
Baseline behavioral quest.		X							
Phone reporting system					X				
Product acceptability quest.*						X		X	
Qualitative hCG	♀	♀	♀		♀	♀		♀	♀
Dipstick UA	X					X		X	▲
CBC	X					X		X	▲
BUN, creatinine, ALT, AST	X					X		X	▲
Syphilis RPR	X	▲				X		X	▲
Confirm syphilis	▲	▲				▲		▲	▲
HIV-1 serology	X	▲				X		X	▲
Confirm. HIV-1	▲	▲				▲		▲	▲
Plasma archive		X							
HBsAG	X								
HSV serology	X								
Urine GC/CT by NAAT	X	▲	▲		▲	▲		▲	▲
Rectal GC/CT by NAAT	X	▲			▲	▲		▲	▲
Rectal microflora		X	X			X			
Rectal cytokines		X	X			X			
Normosol-R enema		X	X			X			
Rectal lavage,effluent, sloughing		X	X			X			
Fecal calprotectin		X	X			X			
Anoscopy and biopsies		X	X		▲	X			
Flex. sigmoidoscopy and biopsies		X	X			X			
Study product*			X		X				
Collect used & unused product*						X		X	▲

▲ If indicated ♀ for females of childbearing potential *for participants in treatment arms