

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

MTN-007

DAIDS Protocol #:10736

**A Phase 1 Randomized, Double-Blinded, Placebo-Controlled Rectal Safety and
Acceptability Study of Tenofovir 1% Gel
Version 1.0/08 April 2009**

**THE AMENDED PROTOCOL IS IDENTIFIED AS:
Version 2.0/August 13, 2010**

CONRAD IND#: 73,382

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-007 study and must be forwarded to your Institutional Review Boards (IRBs) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-007

Summary of Revisions

This amendment incorporates a previously issued Letter of Amendment in addition to the following protocol revisions:

- Modifications to Protocol Team Roster
- Updates to the *List of Abbreviations and Acronyms*
- Update to Background Section to include information regarding the reformulation of tenofovir 1% gel that will be used in MTN-007
- Clarification of Exclusion Criteria
- Updates to Section 6, *Study Product*
- Clarification of study procedures
- Modifications to Section 8, *Assessment of Safety*, to reflect current DAIDS guidelines
- Correction to Section 9, *Clinical Management*
- Updates to Section 13.2, *Protocol Registration*, to reflect new DAIDS Protocol Registration template language
- Modifications to Appendix I: *Schedule of Study Visits and Evaluations*
- Modifications to MTN-007 Schedule of Study Visits and Evaluations for Participants in the Sample Informed Consent (Enrollment) document
- Modification to the Signature Page in the Sample Informed Consent (Storage and Future Testing of Specimens)
- Updates to website links within the protocol

- Other minor editorial and typographical updates and corrections
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Rationale

The primary rationale for the modifications included in this protocol amendment is to update the protocol to reflect recent updates to requirements for Expedited Adverse Event Reporting to the US NIH Division of AIDS, to reflect clarifications to the DAIDS AE Grading Table, and to include information regarding the reformulation of tenofovir 1% gel that will be used in MTN-007. Section 6, *Study Procedures*, is also updated to include a subsection to Section 6.4, *Study Product Supply and Accountability*, to describe the dispensation of male condoms and lubricant and provides guidance in the event a participant reports prohibited medications or practices during study in Section 6.7, *Prohibited Medications and Practices*.

This amendment further clarifies exclusion criterion regarding active rectal or reproductive tract infections as well as study procedures, including additional detail regarding rectal exams and rectal specimen collection.

Updates to the Protocol Team Roster, Protocol Registration template language and Sample Informed Consent documents are also included in this amendment.

Implementation

This amendment is now official MTN-007 protocol documentation. Prior to implementing the revisions listed below, MTN-007 study sites will submit this Summary of Changes and protocol Version 2.0 to all relevant regulatory authorities and IRBs.

Upon receipt of all regulatory and IRB approvals and completion of protocol registration procedures, the protocol modifications listed below will be implemented. With exceptions to modifications to the Protocol Team Roster, detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** (for additions).

Detailed Listing of Revisions

1. The revisions contained in prior Letter of Amendment #01, dated 16 September 2009, have been incorporated into the amended protocol. Because these revisions have been detailed in previous official protocol documentation, they are not also detailed in this Summary of Changes, with exceptions of LoA #01 items 2, 4, 6, 9. A reference copy of the Letter of Amendment is available at: <http://www.mtnstopshiv.org/node/1418>.

LoA #01, item 1: Section 8.4, Expedited Adverse Event (EAE) Reporting Requirements:

As specified in LoA

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 Support Center (RSC) 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 RSC via the electronic reporting system DAERS established by DAIDS. The RSC 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 RSC 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 RSC. Additionally, the RSC 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 RSC 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 RSC website: <http://rsc.tech-res.com> (and MOP, if applicable),

and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please contact the RSC. DAIDS EAE forms should be submitted to DAIDS through the Regulatory Support Center (RSC) Safety Office via email (rscsafetyoffice@tech-res.com) or by calling 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.]

As specified in Version 2.0

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

Requirements, definitions and methods for expedited reporting of Adverse Events (AEs) are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance>.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited AE reporting to DAIDS. In the event of system outages or technical difficulties, expedited AEs may be submitted via the DAIDS EAE Form. For questions about DAERS, please contact DAIDS-ES at DAIDS-ESSupport@niaid.nih.gov. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited AEs by documenting the information on the current DAIDS EAE Form. This form is available on the RSC website: <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

~~The adverse events that must be reported in an expedited fashion to the DAIDS Regulatory Support Center (RSC) 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). Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above may also be considered to be serious.⁹⁷~~

~~All sites will report all EAEs expeditiously to RSC via the electronic reporting system DAERS established by DAIDS.~~

EAE reporting procedures specific to this protocol are that once the sites have submitted EAEs via DAERS (as above), the RSC 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 RSC 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 RSC. Additionally, the RSC 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 RSC update 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:

~~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 RSC website: <http://rsc.tech-res.com> (and MOP, if applicable), and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please contact the RSC. DAIDS EAE forms should be submitted to DAIDS through the RSC Safety Office via email (DAIDSRSCSafetyOffice@tech-res.com) or by calling 1-800-537-9979 or 301-897-1709 or fax 1-800-275-7619 or 301-897-1710.]~~

The SAE EAE Reporting Category, as defined in Version 2.0 of the DAIDS EAE Manual, will be used for this study. The study agents for which expedited reporting to CONRAD and the DAIDS MO are required are: tenofovir 1% gel, 2% nonoxynol-9 gel, placebo gel, and the gel applicator.

Section 8.4, Expedited Adverse Event (EAE) Reporting Requirements, EAE Reporting Period, subsection:

- **The expedited AE reporting period for this study is defined as SAEs (as defined above) must be reported on an expedited basis during the Protocol defined EAE Reporting Period, which is the entire study duration for an individual participant (from study enrollment until the participant's final study contact (Follow-Up Phone Assessment Visit/Termination Visit). In addition, should site staff become aware of any serious, unexpected, clinical suspected adverse drug reactions after the participant's final study contact (Follow-Up Phone Assessment Visit/Termination Visit), such events also will be expeditiously reported.**
- **After the protocol-defined AE reporting period, unless otherwise noted, only suspected unexpected serious adverse reactions (SUSARs) as defined in Version 2.0 of the EAE Manual will be reported to DAIDS if the study staff become aware of the events on a passive basis (from publicly available information).**

LoA #01, item 2: Section 6.2, Administration, second paragraph:

As specified in LoA

~~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 aAt 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.~~

As modified in Version 2.0

Second paragraph, first sentence:

At the Treatment 1 Visit, participants will receive one applicator of their assigned study product for **self-administration** under observation **of the site clinician/designee**.

LoA #01, item 4: Section 5.3, Exclusion Criteria #2, first sentence:

As specified in LoA

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).

As modified in Version 2.0 (including an additional modification to the note to Exclusion Criterion #2):

At screening: ~~history,~~ **participant-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).

Note: In cases of **non-anorectal** GC/CT identified at screening, one re-screening 2 months after screening visit will be allowed

LoA #01, item 6: Section 7.9, Interim Contacts and Visits, Table 16: Interim Contacts and Visits

As specified in LoA:

Urine	<ul style="list-style-type: none">• Collect urine sample*<ul style="list-style-type: none">○ ♀ Qualitative hCG○ Dipstick U/A○ GC/CT
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As modified in Version 2.0:

Urine	<ul style="list-style-type: none">• Collect urine sample*<ul style="list-style-type: none">○ ♀ Qualitative hCG○ Dipstick U/A*○ GC/CT by NAAT*
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LoA #01, item 6: 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:

As specified in LoA:

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

As modified in Version 2.0:

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

LoA #01, item 9: Protocol Team Roster

As specified in LoA

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As modified in Version 2.0

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2. The Protocol Team Roster is updated to reflect current Protocol Team members and updated contact information:

The following individuals are added to the Protocol Team Roster:

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The following individuals have updated contact information:

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The following individuals are removed from the protocol: Nancy Connolly, Debra Mérés, Lisa Noguchi, and Ana Ventuneac

3. The *List of Abbreviations and Acronyms* is updated:

ATP
CAB
~~FHI~~

adenosine triphosphate
community advisory board
~~Family Health International~~

RCC
RSC
T_{max}
TFV

~~Regulatory Compliance Center~~
Regulatory Support Center
time to peak concentration
tenofovir gel

4. *Protocol Summary, Study Regimen*, third sentence:

Participants will return to the clinic, where **they will self-administer** a single dose of the study gel ~~will be administered~~ **under observation**.

5. References to “HEC Placebo Gel” have been changed to “placebo gel” throughout the document
6. In Section 2.1, *Background of Microbicide Research, Developing Safety Standards for Rectally-Administered Microbicides* section, *Intestinal mucosal mononuclear cell phenotype* subsection, second paragraph, second sentence:

~~Samples from the Boston, MA and Birmingham, AL sites will be sent by overnight courier to Pittsburgh.~~

7. In Section 2.3.2, *Strength of Study Product*, first sentence:

The strength of the tenofovir gel will be the concentration (1%) previously tested in HPTN 050 (investigational new drug (IND 55,690)), **CAPRISA 004**, CONRAD A04-095 (IND 73,382) and A04-099 (IND 73,382), HPTN 059 (IND 55,690), MTN-001 (IND 55,690), and MTN-002 (IND 55,690), **and RMP-02/MTN-006 (CONRAD IND 73,382)**.

8. In *new* Section 2.6.1, Reformulated Tenofovir Gel:

Section 2.6.1 Reformulated Tenofovir Gel

The reformulated tenofovir 1% gel being used in MTN-007 has a lower osmolality than the original formulation that was used in prior studies. Additionally, the density of the reformulated tenofovir 1% gel is 1.02 g/mL. This will be the first clinical trial using this formulation of tenofovir 1% gel. Safety testing in epithelial cell lines has demonstrated retention of transepithelial resistance (TER) by Caco-2 and HEC-1-A cell lines. Previous results showed the original formulation to induce a transient drop in the epithelial resistance. This was not observed with the reformulated TFV gel. Safety testing of colorectal explants shows similar MTT (Formazan [1-(4,5-dimethylthiazol-2-yl)-3,5-diphenylformazan]) results with both formulations. However, histological testing showed retention of the epithelium after application of the reformulated TFV gel as compared to epithelial stripping with the original formulation. Additional testing in colorectal explant cultures also showed that the new formulation did not compromise product efficacy. Collectively, these data suggest that the reformulated TFV gel is just as effective as the original formulation but is less toxic to the epithelium.

9. In Section 2.9.1, *Tenofovir 1% Gel*:

Pharmacokinetics sub-section, second paragraph:

In MTN-002, the first microbicide trial to be conducted during pregnancy, 16 women received a single vaginal dose of tenofovir 1% gel prior to elective cesarean section. Tenofovir levels were measured in blood, amniotic fluid, cord blood, endometrial tissue, and placental tissue. Plasma tenofovir levels were compared to historical controls. Study results demonstrated that the PK levels of a single vaginal dose of tenofovir 1% gel in pregnant women was similar to those found in non-pregnant women and that serum tenofovir levels were up to 50 – 100 times less as compared to standard oral dosing. Additionally, tenofovir was shown to get to the fetal compartment with low overall cord levels (~40 times less than oral dosing), but with a similar cord blood: maternal ratio. Overall findings suggest that tenofovir is safe for use in term pregnancy and warrants additional investigation during pregnancy.

Safety sub-section, last two paragraphs:

A Phase 2b study of vaginally-administered tenofovir 1% gel use (CAPRISA 004) has recently completed follow-up and data analysis.⁷⁹ This study, conducted among sexually active, HIV-uninfected women at an urban and rural site in South Africa, compared the safety and effectiveness of tenofovir 1% gel when use within 12-hours before and after intercourse, versus placebo gel (HEC). Safety assessments as well as HIV and urine pregnancy tests were performed at monthly follow-up visits. Pelvic exams were also performed at quarterly visits.

Study results suggest that vaginally-administered, coitally-dependent use of tenofovir 1% gel is safe. No increases in renal, hepatic, pregnancy-related, or genital AEs were observed. Additionally, tenofovir 1% gel was shown to reduce HIV infection by approximately 39% regardless of sexual behavior, condom use, HSV-2 infection, or urban/rural location. It is important to note, however, that the high acceptability rate (~97%) did not correspond to the average adherence rate (~61%). While these data suggest a favorable safety and effectiveness profile for tenofovir 1% gel, further studies must be done to assess whether more frequent (e.g. daily) dosing will enhance adherence and as a result, effectiveness, without compromising participant safety, and whether tenofovir 1% gel is safe, well-tolerated, and efficacious when administered rectally.

10. In Section 2.10, *Justification of No Treatment Arm*, second sentence:

The study will also include a no treatment arm in which mucosal samples will be collected at the same time intervals as the treatment arms; at the **Enrollment/Baseline Evaluation** ~~Visit~~, at the **second Treatment 1** ~~Visit~~ approximately 2 weeks later, and at the **Final** ~~Visit~~ approximately 2 weeks later.

11. In Section 5.2, *Inclusion Criteria*, item 12:

12. **At Screening and Enrollment, M** must agree not to participate in other drug trials, research studies involving drugs, medical devices, or genital products for the duration of study participation (until all follow-up visits are completed)

12. In Section 5.3, *Exclusion Criteria*, item #10:

10. By participant report at screening, use of **post-exposure prophylaxis for HIV exposure**, systemic immunomodulatory medications, rectally administered medications,

rectally administered products (including condoms) containing N-9, or any investigational products within the 4 weeks prior to the Enrollment/Baseline Evaluation Visit and throughout study participation

13. In Section 6.2, *Administration*, second paragraph, last sentence:

Participants will be instructed to insert the gel as close to the same time each day as possible.

14. In Section 6.3.1, *Tenofovir 1% Gel*, first sentence:

Tenofovir 1% gel (weight/weight) is a gel formulation of tenofovir (PMPA, 9-[(R)-2-(phosphonomethoxy)propyl]adenine monohydrate), formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, **and hydroxyethyl cellulose, and with a pH adjusted to 4-5.** Tenofovir 1% gel is a transparent, viscous gel that will be filled into applicators to form pre-filled, single-use applicators.

15. In Section 6.4.3, *Dispensing*, second paragraph:

The participants will be provided with sealable bags to collect and store all used **and unused** applicators, for return to the clinic.

16. In Section 6.4.5, *Male Condoms and Lubricant*:

6.4.5 Male Condoms and Lubricant

All participants will receive male condoms and participants in the treatment arms will be offered study specified lubricant to aid with applicator insertion. The condoms and lubricant will be dispensed by the clinic staff, and made available in the clinic.

17. In Section 6.5, *Assessment of Participant Adherence*, eighth, and ninth sentences:

Eight and ninth sentences:

When participants do not call the system **within** 48 hours, an alert is automatically generated and sent by email to a staff member at Columbia University ~~and~~. **The staff member at Columbia University will then contact** the study coordinator at the study site who then contacts the participant to inquire about missed calls (if the participant forgot to call) and adherence to the study product regimen.

18. In Section 6.7 *Prohibited Medications and Practices*, second and third sentences:

Furthermore, study participants will be advised not to use the following products within 4 weeks of the Enrollment/**Baseline Evaluation** Visit and throughout study participation: **post-exposure prophylaxis for HIV exposure**, systemic immunomodulatory medications, rectally administered medications, rectally administered products containing N-9, or any other investigational products. ~~Should participants report use of any of these medications or products, they will be required to discontinue use of study product, but will continue to complete all scheduled study visits.~~ **PSRT consultation will be requested regarding use of study product. In the event that a participant reports NSAID use prior to a visit requiring endoscopy or biopsy, the study visit should be rescheduled where possible.**

If not, the determination of action must be decided via an emergency PSRT consultation.

19. All changes made in Section 7 as listed below, have been updated accordingly in Appendix I: Schedule of Study Visits and Evaluations.

20. In Section 7, *Study Procedures*:

- Screening (Visit 1)
- Enrollment/Baseline Evaluation (Visit 2)
- Treatment/~~Follow-Up Phone Call~~ (Visit 3)
- **Follow-Up Phone Assessment (Visit 4)**
- Treatment 2 (Visit 4-5)
- Final (Visit 5-6)
- Follow-up Phone Assessment/**Termination Visit** (Visit 6-7)

21. In Section 7, *Study Procedures, Rectal Specimens*, anorectal swabs has been changed to **rectal** swabs to maintain consistency in the document.

22. In Section 7, *Study Procedures, Clinical*, text has been added to include treatment or referral for UTIs/RTIs/and STIs if clinically indicated. Appendix VII: *Sample Informed Consent Document (Enrollment)* have been updated accordingly.

23. In Section 7, *Study Procedures, Urine*, has been updated to clarify that all GC/CT testing will be performed by NAAT.

24. In Section 7, *Study Procedures, Clinical*, Reinforce Counseling has been changed to **Provide** Counseling.

25. In Section 7.1, *Screening Visit, Table 8: Screening Visit*:

Clinical, second bullet:

- **Document pre-existing conditions**

Blood, Collect blood specimens, second sub-bullet:

- BUN, creatinine (**calculate creatinine clearance**), ALT, AST

26. In Section 7.2, *Enrollment/**Baseline Evaluation** Visit*:

The Enrollment Visit (Day 0) will occur within 36 days of the Screening Visit.

27. In Section 7.2, *Enrollment/**Baseline Evaluation** Visit, Table 9: Enrollment/**Baseline Evaluation** Visit (Day 0, Within 36 Days of Screening Visit)*:

Administrative, fourth bullet:

- Eligibility ~~assessment~~ **confirmation**

Clinical, seventh bullet, second sub-bullet:

- HIV **pre-and** post-test*

Rectal Specimens, first bullet:

- Collect Rectal swabs for microflora
 - **Rectal swab for microflora**
 - **Rectal GC/CT by NAAT***

28. In Section 7.3, *Treatment 1 Visit*, Table 10: *Treatment 1 Visit*:

Clinical, *Provide counseling* bullet, first and last sub-bullets:

- ~~Reinforce~~**Provide** counseling
 - Adherence (protocol) **including RAI abstinence**
 - ~~Protocol adherence, including RAI abstinence~~

Rectal Specimens, first bullet:

- Rectal swabs for microflora
 - **Rectal swab for microflora**
 - **Rectal GC/CT by NAAT***

Study Product Supply:

- **Observe participant Administration of** single dose of tenofovir 1% gel, 2% N-9 gel, or ~~HEG~~-placebo gel **and offer study lubricant** to participants in treatment arm

29. Throughout the protocol and in Section 7.4, *Follow-up Phone Call*, heading and table title is changed to *Follow-up Phone Assessment* for consistency and the first sentence:

A follow-up phone **assessment** will be scheduled to take place within **approximately 24** hours of the Treatment 1 Visit.

Table 11: Follow-up Phone Call **Assessment**

30. In Section 7.5, *Treatment 2 Visit*, Table 12: *Treatment 2 Visit*:

Behavioral Assessment, first bullet:

- ~~Instruct participants randomized to treatment arm~~ **Provide instructions** on use of Phone Reporting System **to participants randomized to treatment arm**

Study Product Supply:

- Provide supply of tenofovir 1% gel, 2% N-9 gel, or ~~HEG~~-placebo gel **and offer study lubricant** to participants in treatment arm

31. In Section 7.8, *Follow-up Procedures for Participants Who Discontinue Study Product*, first sentence:

Participants who ~~temporarily or~~ permanently discontinue study product will not routinely be withdrawn from the study.

32. In Section 7.8, *Follow-up Procedures for Participants Who Discontinue Study Product*, subsections 7.8.1 – 7.8.4:

- Anoscopy (**only if clinically indicated**)
- Flexible sigmoidoscopy (**only if clinically indicated**)

33. In Section 7.8.4, *Participants Who Are Discontinued from Study Product by the Site Investigator*, Table 15: *Early Termination Visit, Administrative, Clinical, and Study Product* :

Administrative, first bullet:

- ~~Review/update demographic information~~

Clinical, fourth and fifth bullets:

- Perform physical exam*
- Perform rectal exam*

34. In Section 7.9, *Interim Contacts and Visits*:

Administrative, first bullet:

- ~~Review/update demographic information~~

Clinical, sixth bullet:

- ~~Reinforce~~ **Provide** counseling

35. In Section 7.11, *Clinical Evaluations and Procedures*, *Rectal Exam* subsection:

Rectal Exam and Rectal Specimen Collection

The participant will be positioned in the left lateral decubitus position for the following procedures:

Rectal Exam

- ~~Rectal swabs microflora and GC/CT and sponge collection for cytokines: A lubricated plastic anoscope will be gently and fully inserted (until the lateral ‘wings’ touch the anal margin) and the obturator removed. Swabs for microflora and GC/CT will be sequentially inserted through the anoscope and placed in contact with the rectal wall, turned through 360 degrees and removed. Next, the two sponges will be inserted through the anoscope and placed in contact with rectum and remain there for 5 minutes. The sponges will then be removed and packaged, then the anoscope will be slowly removed.~~
- **Visual and Digital rectal examination: The examiner will conduct a visual examination of the anus and surrounding area and note any abnormality.** The examiner will **then** insert a lubricated gloved finger into the anal canal and sweep around the internal anal circumference.

Rectal Specimen Collection

- **Rectal swabs GC/CT, microflora, and sponge collection for cytokines: A lubricated plastic anoscope will be gently and fully inserted (until the lateral ‘wings’ touch the anal margin) and the obturator removed. Swabs for GC/CT and microflora will**

be sequentially inserted through the anoscope and placed in contact with the rectal wall, turned through 360 degrees and removed. Next, the sponge will be inserted through the anoscope and placed in contact with rectum and remain there for 5 minutes. The sponge will then be removed and packaged, then the anoscope will be slowly removed

- Rectal lavage: A 1250 mL Normosol-R® (Hospira Inc., Lake Forest, IL) enema will be inserted through the anus and the contents squeezed into the rectum. The participant will hold the fluid in the rectum for approximately 5 minutes then expel it, including stool, into a collection device placed over a toilet bowl-
- Flexible sigmoidoscopy and biopsy: A flexible sigmoidoscope will be inserted to 15 cm and biopsies taken using biopsy forceps-
- Anoscopic biopsy: A lubricated anoscope will be inserted into the anorectum until the 'wings' touch the anal verge. Biopsies will be taken at 9 cm using biopsy forceps.

36. In Section 7.13.3, *Genova Diagnostics*:

Fecal specimens will be collected and shipped to Genova Diagnostics for analysis.

37. In Section 8.3.1, *Adverse Events*, the third paragraph, first sentence:

The site IoR will determine AE resolution or stabilization in their best clinical judgment, but may seek DAIDS MO and/or ~~SMC-PSRT~~ medical consultation regarding follow up or additional evaluations of an AE.

38. In Section 8.3.2, *Serious Adverse Events*, first sentence:

Serious adverse events (SAEs) will be defined by ~~per CFR 312.32~~, **the** Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010) as AEs occurring at any dose that:

39. In Section 8.3.3, *Adverse Relationship to Study Product*:

First sentence:

The relationship of all AEs to study product will be assessed per the Manual for Expedited Reporting of Adverse Events to DAIDS (**Version 2.0**, dated ~~6 May 2004~~ **January 2010**), the tenofovir gel investigator's brochure, the N-9 package insert, HEC Placebo Gel investigator's brochure, and clinical judgment.

Bullet points:

- ~~*Definitely r*Related:~~ ~~adverse event and administration of study agent are related in time, and a direct association can be demonstrated with~~ **There is a reasonable possibility that the AE may be related to the study agent(s)**
- ~~*Probably related:*~~ ~~adverse event and administration of study agent are reasonably related in time, and the adverse event is more likely explained by the study agent than by other causes~~

- ~~Possibly related:~~ adverse event and administration of study agent are reasonably related in time, and the adverse event can be explained equally well by causes other than the study agent
- ~~Probably not related:~~ a potential relationship between administration of study agent and adverse event could exist, but is unlikely, and the adverse event is most likely explained by causes other than the study agent
- **Not related:** the adverse event is clearly explained by another cause unrelated to administration of the study agent. Reportable events must have documentation to support the determination of “not related.” **There is not a reasonable possibility that the AE is related to the study agent(s)**

40. In Section 8.5, *Pregnancy and Pregnancy Outcomes*, subject(s) has been changed to **participant(s)** throughout the section to maintain consistency with the protocol document.

41. In Section 8.5, *Pregnancy and Pregnancy Outcomes*, second paragraph, second sentence:

Pregnancy outcomes will not be expeditiously reported to CONRAD and the DAIDS MO unless there is an associated adverse event in the pregnant participant that meets expedited reporting criteria or the pregnancy results in a congenital anomaly meeting the **ICH Manual for Expedited Reported of Adverse Events to DAIDS (Version 2.0, January 2010)** guidelines for expedited reporting.

42. In Section 9, *Clinical Management*:

Guidelines for clinical management and product ~~hold~~/discontinuation are outlined in this section.

In general, the site investigator has the discretion to ~~hold~~-**discontinue** study product at any time if she/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the investigator should immediately consult the PSRT ~~for further guidance on resuming study product, continuing the hold temporarily, or progressing to~~ **regarding** permanent discontinuation.

The site investigator or designee will document all ~~product holds and~~ discontinuations on applicable case report forms.

43. In Section 9.3, *Discontinuation of Study Product(s) in the Presence of Toxicity*, Grade 3 subsection:

Grade 3

Participants who develop a Grade 3 AE or toxicity that is not specifically addressed below and is judged to be ~~possibly, probably, or definitely~~ related to study product should have that study product permanently discontinued.

44. In Section 9.5, *Management of Specific Adverse Events*:

~~Specific product hold requirements are specified here in the context of clinical management of adverse events.~~

45. In *old* Section 11.4, Study Activation:

11.4 Study Activation

~~Following IRB review and approval, all study sites will complete DAIDS Protocol Registration procedures in accordance with the current DAIDS Protocol Registration Policy and Procedures Manual available at:~~

~~(<http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/ProtocolRegPolicy.pdf>).~~

~~Pending successful protocol registration, submission of all other required study activation documents to the MTN CORE, and DAIDS approval, MTN CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site by the MTN CORE.~~

46. In Section 13.2, *Protocol Registration*:

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent forms(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

~~Following IRB review and approval and prior to implementation of this protocol, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.~~

~~Pending successful protocol registration, submission of all other required study activation documents to the MTN CORE, and DAIDS approval, MTN CORE staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site by the MTN CORE.~~

~~Each study site will complete protocol registration with the DAIDS RCSC Protocol Registration Office. For additional information **on the protocol registration process and specific documents required for amendment registration**, refer to the **current** protocol registration documents located at <http://rsc.tech-res.com/protocolregistration/>~~http://rec.tech-res.com/forms.htm~~. Protocol registration must occur as a condition for site specific study activation; no participants may be screened or enrolled in this study prior to obtaining protocol registration approval and completing all other study activation requirements. MTN CORE (FHI) staff will notify each study site when all activation requirements have been met by issuing a site specific study activation notice. Study implementation may not be initiated until the activation notice is issued.~~

Site-specific informed consent forms (ICFs) WILL NOT be reviewed or approved by the DAIDS PRO, and sites will receive an Initial Registration Notification when the DAIDS PRO receives a complete registration packet. Receipt of an Initial Registration Notification indicates successful completion of the protocol registration process. Sites will not receive any additional notifications from the DAIDS PRO for the initial

protocol registration. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

~~The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chairs and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s) and the RCC prior to implementing the amendment.~~

47. In Section 13.3.1, *Risks, Enemas*, second sentence:

A hollow tube about the thickness of a pencil will be used to put approximately 1250 mL of Normosol-R pH 7.4 into the rectum and flush it out again (a larger volume may be required if the initial volume does not produce results), along with any stool that is there.

48. In Section 13.5, *Participant Confidentiality*, bullets:

- **Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH**
- ~~DAIDS, NIMH, and/or its contractors, including study monitors~~
- Representatives of CONRAD
- Representatives of the MTN CORE, SDMC, and NL
- ~~The US FDA~~
- ~~Office for Human Research Protections (OHRP)~~
- Site IRBs

49. In Section 14, *Publication Policy*, second sentence:

Any presentation, abstract, or manuscript will be submitted by the Investigator to the MTN

Manuscript Review Committee, DAIDS, **NIIMH**, and CONRAD, for review prior to submission.

50. The listing of the DAIDS AE Grading Table is updated throughout the protocol to include the clarification dated August 2009:

DAIDS AE Grading Table, Version 1.0, December 2004 (**Clarification dated August 2009**)

51. All references to the Regulatory Compliance Center have been updated throughout the protocol to reflect the new operating name, Regulatory Support Center:

52. In Appendix VI: Sample *Informed Consent Document (Screening)*:

Introduction, second sentence:

This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) **and CONRAD**.

What Do I Have To Do If I Take Part In The Screening Exams and Tests:

Second bullet:

- Answer questions about yourself, such as where you live, your education, your behavior, including your sexual behavior, your medical history, ~~menstrual period history~~, and any medicines that you may take and how we can contact you. **Women will also be asked about menstrual cycle history.**

Seventh bullet:

- Provide a urine sample to be tested for pregnancy (**females**) and urinary tract and sexually transmitted infections

What About Confidentiality?, bullets:

- **Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH**
- ~~The US Food and Drug Administration (FDA)~~
- ~~US National Institutes of Health (NIH)~~
- ~~Office for Human Research Protections (OHRP)~~
- [INSERT NAME OF SITE] IRB
- Study staff
- ~~Study monitors~~
- CONRAD (the company that supplies the gel used in this study)

53. In Appendix VII: *Sample Informed Consent Document (Enrollment)*:

Introduction, second sentence:

This Microbicide Trials Network (MTN) study is sponsored by the US National Institutes of Health (NIH) **and CONRAD**.

What Do I Have To Do If I Am In This Study? section, second paragraph, second and third sentences:

You will answer questions about your sexual practices and will answer some questions about your medical and ~~menstrual~~ history to make sure you are still eligible to join this study. **Women will also be asked about menstrual cycle history.**

At most visits, we will ask you to do the following, sub-section:

- **Receive test results from previous visits, if available**

At the Treatment 1 and Treatment 2 Visits, if you are in the group that receives the study gel, you will, sub-section:

- ~~Receive~~ **Self-administer** one dose of the study gel ~~at the clinic under the observation of study staff.~~ **You will also receive study lubricant to make it easier to insert the applicator.** (Treatment 1 Visit)
- Receive a 7-day supply of study gel **and study lubricant** (this will be the same study gel that you received at the first treatment visit). (Treatment 2 Visit)
- Call an automated phone system each time you use the gel at home. **You should insert the gel as close to the same time as possible, before your longest period of rest.** When you call, you will be asked a brief set of questions. You will learn how the phone system works, and about the compensation you will receive for the calls. You will also have the opportunity to try the phone system out and ask any questions you may have. **You may be contacted by the study staff if you miss a phone call** (Treatment 2 Visit)

Final Visit sub-section, first bullet:

- If you are in the group that receives the study gel, answer questions about your experience using the study gel, including ~~questions about your sexual behavior~~ **what you did and did not like about the gel**

Final Visit sub-section, first bullet:

- You will be asked to return ~~any~~ **all** used and unused applicators to the study clinic

At Any Time In the Study sub-section:

If the study doctor thinks you have health problems that may be caused by infections, including those passed through sex, or if you have signs of infections, including those passed through sex, you may:

- **Have a physical or rectal exam**
- **Give blood, urine, rectal fluid, or rectal tissue samples to test for infections**

- Provide a urine sample for a pregnancy test (women)
- Get treatment or referrals for most types of infections if you need it

What About Confidentiality?, bullets:

- Representatives of the US Federal Government, including the US Food and Drug Administration (FDA), the US Office for Human Research Protections (OHRP), NIH, and/or contractors of the NIH
- ~~The US Food and Drug Administration (FDA)~~
- ~~US National Institutes of Health (NIH)~~
- ~~Office for Human Research Protections (OHRP)~~
- [INSERT NAME OF SITE] IRB
- Study staff
- ~~Study monitors~~
- CONRAD (the company that supplies the gel used in this study)

MTN-007 Schedule of Study Visits and Evaluations for Participants has also been updated to accurately reflect the procedures and evaluations detailed in Section 7 and Appendix 1 of the protocol

54. In Appendix VIII: *Sample Informed Consent Document (Storage and Future Testing of Specimens)*:

How Will You Use My Sample? Section, seventh, eighth, and ninth sentences:

~~If a rare situation came up where the researchers decided that a test result would provide important information for your health, the researchers would tell your study doctor and your study doctor would try to contact you. If you wish to be contacted with this type of test result, you must give the study doctor or nurse any change to your address and/or phone number. If you want your regular doctor to be told about this type of test result, you must provide the study doctor or nurse with your regular doctor's name, address and phone number.~~

Signature Page:

~~If you have read the informed consent (or had it read and explained to you), and all your questions have been answered and you agree to this specimen storage and future testing, please sign your name below. Please carefully read the statements below and think about your choice. No matter what you decide it will not affect your participation in the MTN-007 study or your medical care. Please initial or mark your choice and sign your name below.~~

I agree to allow my leftover samples to be stored for future testing.

OR

I do not agree to allow my leftover samples to be stored for future testing.

55. The version number and date are updated throughout the protocol document

56. Correction of minor editorial and typographical edits and updates are made throughout the protocol document