Microbicide Trials Network
LETTER OF AMENDMENT #01 TO:

RMP-02/MTN-006
DAIDS Document ID #10769

A two-site, Phase 1, partially-blinded, placebo-controlled safety, acceptability, and pharmacokinetic trial of topical, vaginally-formulated tenofovir 1% gel applied rectally compared with oral 300 mg tenofovir disoproxil fumarate in HIV-1 seronegative adults

Version 1.0/07 April 2009

CONRAD IND # 73, 382

Letter of Amendment Date: 17 August 2009

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the RMP-02/MTN-006 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 RMP-02/MTN-006.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for RMP-02/MTN-006. This LoA provides clarification on the following items:

1. Modifications to Section 8 to update communication pattern regarding adverse event and pregnancy reporting. These changes do not impact the degree or details of safety reporting in RMP-02/MTN-006
2. Inclusion of additional rectal microflora sampling time point per FDA request
3. Elimination references to INR and PTT in Section 5.3, Exclusion Criteria, as they are not included in the Screening Procedures
4. Removal of excessive detail regarding sponge types in the protocol that could potentially be in conflict with the details provided in the RMP-02/MTN-006 SSP manual
5. Clarifications to the informed consent documents to achieve consistency with the protocol

6. Other minor corrections and updates

Section 2: Implementation

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

1. **The following changes are made to Section 8, Assessment of Safety to reflect the guidelines put forth in the RMP-02/MTN-006 Clinical Trials Agreement.**

Section 8.1, Safety Monitoring, second paragraph, first sentence:

First sentence:

The DSMB will be comprised of the Chair, who will be an MD/DO, a representative from UCLA and from Pittsburgh/Magee, one of which may be the Chair, ~~CONRAD MO,~~ and a Biostatistical Representative.

Section 8.1, Safety Monitoring, second paragraph, first sentence:

For all DSMB meetings, there will be an open session accessible to all interested parties, followed by a closed session, limited to DSMB members only. The RMP Regulatory Core will file a summary report of DSMB recommendations with DAIDS, CONRAD, and Gilead after each DSMB meeting.

Section 8.2, Clinical Data Safety Review, second paragraph:

The U19 MDP Regulatory staff (Core B) will review incoming safety data on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. Adverse event reports requiring expedited handling will be submitted by ~~the Regulatory Core within 3 business days to:~~ **each participating study site to the DAIDS RCC Safety Office (via DAIDS Adverse Events Reporting System DAERS), and RCC will in turn distribute reports to the DAIDS Medical Officer, CONRAD Medical Officer, and Gilead (when the reports are related to the Gilead study product (i.e. oral tablets)), as well as UCLA/Pitt IRBs and RMP staff for review.**

- ~~DAIDS MO~~
- ~~CONRAD~~
- ~~Gilead~~
- ~~Site IRBs~~
- ~~RMP staff~~

When indicated, the FDA will be notified through CONRAD (the IND holder). **See Section 8.4 for complete description of this process.**

Section 8.2, Clinical Data Safety Review, last paragraph:
In the unlikely event that the protocol team or DSMB has serious safety concerns that lead to a decision to permanently discontinue study products for all participants and stop accrual

into the study, the protocol team or DSMB will request a review of the data by the DAIDS **and CONRAD** Medical Officer**s** before recommending that the study be stopped. If at any time, a decision is made to discontinue one or more study products in all participants, ~~DAIDS will notify~~ CONRAD ~~who~~ will notify the US FDA and the site investigators of record will notify the responsible IRBs expeditiously.

Section 8.4, Expedited Adverse Event Reporting Requirements:

Expedited Adverse Event (EAE) Reporting

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 the 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.[83]

All sites will report all SAEs expeditiously to RCC via the electronic reporting system DAERS established by DAIDS. For those reports related to the Gilead study product (i.e. oral tablets), the RCC Safety Office will send the unprocessed reports directly to Gilead. However, the RCC Office will also prepare the draft safety reports for all study products and send them to the DAIDS Medical Officer and CONRAD MOs for review.

Study sites will be contacted by DAIDS MO if any further information or clarification is needed after the report is evaluated by DAIDS and CONRAD MOs. The RCC 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 Gilead, CONRAD, and the RCC. Additionally, the RCC Safety Office will distribute the final safety reports to all DAIDS funded networks/sites evaluating the study products used in this study.

For all SAEs submitted, sites must file an ~~initial 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 **noted**.

EAE Reporting Requirements for this Study

~~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 Expedited Adverse Event (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 then 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, the RCC (to be placed in the file) and Gilead.~~ **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-intl.com (and MOP if applicable), and submitted as specified by the DAIDS EAE Manual. For questions about EAE reporting, please continue to contact the RCC. DAIDS EAE forms should be submitted to DAIDS through the RCC Safety Office (rccsafetyoffice@tech-res.com) or call 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, last paragraph:

In addition, the U19 MDP Core C – Data Management and Biostatistics Core – will file a quarterly report of all pregnancies with CONRAD and Gilead, as well as an annual summary report of all adverse events for the annual IND reports (to be submitted by CONRAD).

2. **The protocol is updated to include an additional rectal microflora swab at Visit 11 per a request from the FDA:**

Table 18: Visit 11 (Study Product Visit #3: Dispense Self-Administered Gel Supply):

Rectal Specimens	• **Anorectal swabs** o **Rectal microflora** • Rectal Sponges o Rectal tenofovir concentrations ~~(dry sponge)~~

Section 2.11, Justification of Sampling Timepoints, Table 9: Schedule of Study Endpoints

Visit 11: Begin 7-day Topical	Blood, fluids from sponges ***					✓						✓	✓	✓		

Appendix I: Schedule of Study Visits and Evaluations:

Rectal microflora			X				X				**X**	X	X		

3. **Section 5.3, Exclusion Criteria, item 3i is modified. This statement is removed as these labs are not being performed at the Screening Visit:**
   i. History of bleeding problems ~~(i.e. INR > 1.5× the site laboratory ULN or PTT > 1.25× the site laboratory ULN)~~

4. **Excessive detail regarding sponge types (i.e., dry vs. pre-moistened) has been removed from Sections 7.2, 7.3, 7.4, and 7.5 of the protocol.**

5. The Sample Informed Consent Document (Enrollment) is modified to achieve consistency with the protocol:

What Do I Have To Do If I Am In This Study? section:

Third paragraph:

Study visits will take about 45 minutes and **can** last up to ~~three~~ **five** hours.

Fourth paragraph, first bullet:

~~Have samples of fluid from your rectum taken to test for gonorrhea and chlamydia~~

Schedule of Study Visits and Evaluations (from Sample Informed Consent Document (Enrollment):

Pregnancy test	X	X	**X**				**X**				X	**X**			▲

Syphilis test	X											**X**			▲

6. In addition to the changes listed above, the following minor clarifications and corrections have been made to the protocol:

Section 2.11 Justification of Sampling Time Points, third paragraph, first sentence:

PK time points will consist of a 4-point extracellular and intracellular plasma and rectal secretion sampling strategy (for women, cervicovaginal secretions will also be collected) within the first 24 hours of oral and single and multiple dose topical exposure for all subjects (Visit 3, Visit 7, and Visit 1~~1~~**2**).

All references to urinalysis are corrected to reflect inclusion of testing for nitrites, not nitrates:

Section 7.1, Screening Visit, Table 13: Visit 1 (Screening Visit):

Urine	• Collect urine sample o ♀Qualitative hCG o Dipstick Urinalysis (UA) for protein, glucose, nitr~~a~~**i**tes, and leukocyte esterase o Nucleic acid amplification test (NAAT) for GC/CT

Section 7.12.1, Local Laboratory Testing, Clinical: Safety Urine Samples, second sentence:

These will include routine urinalysis (protein, glucose, nitr~~a~~**i**tes, and leukocyte esterase), NAAT for GC/CT as well as pregnancy tests for female participants.

Section 13.9.2, Care for Participants Identified as HIV-Infected, second sentence is updated to reflect that both HIV-infected men and women will be referred to appropriate sources of care:

According to site SOPs, study staff will refer participants found to be HIV-infected to available sources of medical and psychological care, social support, and local research studies for HIV-infected ~~women~~ **adults**.

Appendix 1: Schedule of Study Visits and Evaluations:

Test results		X	X				X				X	X			
Schedule next study visit	▲	X	X	X	X	X	X	X	X	X	X	X	~~X~~	▲	▲
CBC w/ diff and platelets	X	**X**	X				X					X			
Vaginal sponge ~~(dry)~~		X	X	X	X	X	X	X	X	X	X	X	X		
TFV levels in rectal mucosal tissue homogenates		**X**	X		X	X	X		X	X		X			
Rectal tenofovir concentrations		~~X~~	X	X	X	X	X	X	X	X	X	X	X		

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