LETTER OF AMENDMENT #01 TO:

MTN-001
DAIDS Document ID 10617

Phase 2 Adherence and Pharmacokinetics Study of Oral and Vaginal Preparations of Tenofovir

Version 2.0 /03 September 2008

IND # 55,690

Letter of Amendment Date: 07 July 2009

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-001 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-001. You will be required to submit IRB/EC correspondence and approved informed consent forms to the DAIDS Protocol Registration Office for informational purposes; however, you will not receive an approval notification from the DAIDS Protocol Registration Office for the LoA.

Summary of Revisions and Rationale

This LoA adds rectal swabs to assess tenofovir concentration in rectal fluid as an optional procedure at the Bronx-Lebanon Hospital Center CRS. Changes previously noted in MTN-001, Version 2.0, Clarification Memo (CM) # 01 are also included in this LoA. The Protocol Team Roster is also updated.

Implementation

This LoA is official MTN-001 protocol documentation. Prior to implementing the revisions listed below, study sites will submit this LoA to all relevant regulatory authorities and the IRB/EC. The Division of AIDS Regulatory Affairs Branch will submit this LoA to the United States Food and Drug Administration for inclusion in Investigational New Drug (IND) application # 55,690.

Upon receipt of all required regulatory and IRB/EC approvals, the protocol revisions listed below will be implemented.

With the exception of modifications to the Protocol Team Roster, text to be deleted is indicated by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

1. The following items were previously noted in MTN-001, Version 2.0, CM #01, dated 3 February 2009:

In Section 7.4, Follow up Procedures for Participants who Discontinue Study Product, the following clarification is made at the end of the first paragraph:

During periods of temporary study product hold or permanent discontinuation, documentation of the last three doses of study product is not required. In addition, the procedures below will be performed as specified within the 6-week study period in which the hold/discontinuation is implemented. These procedures will then be discontinued until study product use resumes (in the case of a temporary hold):

- **Adherence, behavioral, and intravaginal practices assessment will be performed at the next Mid-study or End-of-Study Period Visit, whichever comes first**

- **Acceptability assessment and study product sharing assessment will be performed at the End-of-study Period Visit**

In Section 7.8.3, Pharmacokinetic Procedures: Intensive PK Participants (US Sites), third paragraph, first sentence clarifies that the second randomization will be done within all of the US sites participating in Intensive PK portion of the study:

> For the Intensive PK cohorts at US sites, the End of Study Period sample timing will require a second randomization which will be stratified within each of the ~~two~~ **four** sites.

In Section 10.5, Randomization Procedures, the second paragraph, last sentence, clarifies that the second randomization will be done within all of the US sites participating in Intensive PK portion of the study and is updated to specify that the Intensive PK cohort will be at the US sites to maintain consistency within the protocol:

For the intensive PK cohorts at ~~domestic~~ **US** sites, the end of study period sample timing will require a second randomization which will be stratified within each of the ~~two~~ **four** sites.

2. The Protocol Team Roster is updated to reflect changes to the Protocol Team.

The following addition is made to the Protocol Team Roster:

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The following listing is deleted from the Protocol Team Roster: Roshini Govinden

3. The protocol is updated to reflect the collection of rectal fluid samples to assess tenofovir levels in a subset of participants at the Bronx-Lebanon Hospital Center (BLHC) CRS. The following changes have been made throughout the protocol to reflect this addition:

In Section 2.5.2, Tenofovir 1% Gel, Pharmacokinetics subsection, last paragraph:

A recent macaque study performed by the International Partnership for Microbicides has indicated that vaginal dosing of tenofovir results in tenofovir concentrations which are rapidly detectable (less than one hour after dosing) in the rectal lumen, though at lower concentrations than appeared at the vaginal dosing site (Jeremy Nuttall, personal communication at 2009 MTN Annual Meeting, Arlington, VA, April 21; Accepted Abstract 1050, 2009 National HIV Prevention Conference "The Pharmacokinetics of Tenofovir Following Intravaginal and Intrarectal Administration of Tenofovir Gel to Rhesus Macaques"). A similar finding was noted with rectal dosing of tenofovir and rapidly detectable vaginal concentrations in macaques.

In Section 2.7.2, Rationale, Pharmacokinetics subsection, last paragraph:

Although the mechanisms of the recent IPM findings (see Section 2.5.2) regarding detection of tenofovir concentrations when applied intravaginally or intrarectally in the opposite compartment are not clear, they may include the following:

(1) direct diffusion through tissue
(2) countercurrent concentrating effect related to the close proximity of draining veins and feeding arteries in the female genital tract that are in common (in places) with the rectal arterial supply. The principle is similar to the concentrating effect in the descending and ascending renal tubules. This peri-uterine countercurrent concentrating action has been demonstrated for prostaglandins in the past
(3) macaques groom themselves and may introduce drug from the site of application to the site of sampling

If this finding holds true in humans, it has major implications for future studies as well as use once a microbicide becomes widely available as it suggests that dual site dosing (vaginal and rectal) in those for whom dual site HIV exposures are possible

may be unnecessary, depending on the concentrations achieved in each site with a single route of dosing.

In Section 7.3, Follow-up Visits, Table 7: End of Study Period Visit:

Rectal Specimens	• **Collect rectal fluid for tenofovir level (within 15 minutes following vaginal sampling, Bronx-Lebanon Hospital Center CRS only)**

*If indicated (see also MTN-001 SSP Manual)~~, **Intensive PK/Sub-study (US sites) participants only (see also Section 7.8)~~

In Section 7.8.3, Pharmacokinetic Procedures, Intensive PK Participants (US Sites), third paragraph, second and third bullets:

- Blood, cervical cells (cytology brush), CVL fluid, **rectal fluid,** and vaginal biopsies will be collected according to the schedule outlined in the table below.

- At these three visits, participants will take their assigned dose of oral and/or vaginal tenofovir at the clinic and will undergo collection of their blood, cervical cells, CVL fluids, and vaginal biopsy within 15 – 30 minutes of the assigned sampling time, either pre-dose **or** 2, 4, or 6 hours post-dose. **Participants at the Bronx-Lebanon Hospital Center CRS who opt to have rectal fluid samples taken, will have these samples taken after (within 15 minutes) the vaginal specimens are taken.**

In Section 7.8.3, Pharmacokinetic Procedures, Intensive PK Participants (US Sites), Table 12: Intensive PK Participants Only (US site participants only):

Rectal Fluid (Bronx-Lebanon Hospital Center CRS only)	**Group M**		**Group N**	**Group O**	**Group P**	

In Section 7.8.3, Pharmacokinetic Procedures, Intensive PK Participants (US Sites), end of section:

Rectal fluid samples will be analyzed for tenofovir in a subset of participants at the Bronx-Lebanon Hospital Center CRS. Rectal fluid samples will be collected at the End of Study Period Visits once all vaginal specimens have been collected.

In Section 7.9.3, Network Laboratory Testing, end of section:

Rectal Fluid

- **Tenofovir level in a subset of participants at the Bronx-Lebanon Hospital Center CRS**

In Section 13.3.1, Risks, end of section:

Participants who elect rectal fluid collection may experience mild discomfort in addition to a slight risk of bleeding.

In Appendix I: Schedule of Study Visits and Evaluations:

Rectal swabs (subset of participants				**++**			**++**			**++**		

The following changes are also made to Appendix VII, Sample Informed Consent Document (Enrollment):

End of Study Period Visits for Intensive PK (6-Week, 13-Week, and 20-Week):

- ***For participants at the Bronx-Lebanon Hospital Center site: The rectal fluid samples will be taken at the End of Study Period Visits. A short (approximately 3 ½ inch length) and narrow (approximately 1 ½ inch diameter) hollow plastic tube called an anoscope will be used to help collect the rectal fluid samples. You will lie on your side and the anoscope will be placed gently into your rectum, and two special swabs used to collect fluid will be placed in the anoscope. A small amount (less than 1 teaspoon) of lubricant will be used to help insert the anoscope. You will remain on your side with the swabs and anoscope in your rectum for about 5 minutes. The swabs and anoscope will then be removed from your rectum. These procedures will only be done if you agree to provide these samples. These procedures are being done to see if tenofovir gel, when inserted into the vagina, can pass into the rectum. A recent study in monkeys showed that this might be possible. We would like to see if the same is possible in humans and, how much tenofovir, if any, is passed from the vagina to the rectum.***

What Are The Risks Of This Study? section:

Risks of Rectal Fluid Collection
You may experience some mild discomfort and a small risk of bleeding when your rectal fluid samples are collected.

Will I Receive Any Payment? section, last sentence:

[For Bronx-Lebanon Hospital Center participants]: If you agree to have rectal fluid samples taken from you, you will receive additional compensation [insert amount] for your time and consideration for these samples.

Signature form:

Please mark one of the following boxes if you are asked to have rectal fluid samples taken from you [For Bronx-Lebanon Hospital Center participants]:

____I agree to have rectal fluid samples taken from me

____I do not agree to rectal fluid samples taken from me

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