LETTER OF AMENDMENT #01 TO:

MTN-002
DAIDS Document ID 10600

Phase I Study of the Maternal Single-Dose Pharmacokinetics and Placental Transfer of Tenofovir 1% Vaginal Gel among Healthy Term Gravidas

Version 1.0 / 29 August 2007

IND # 55,690

Letter of Amendment Date: 24 March 2008

Information/Instructions to Study Sites from the Division of AIDS

The information contained in this Letter of Amendment (LoA) impacts the MTN-002 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 IRB/EC is 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-002. 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. Failure to submit IRB/EC correspondence and approved informed consent forms to the DAIDS Protocol Registration Office will result in delays in being able to order study product.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-002.

This LoA adds an exclusion criterion to the MTN-002 protocol and excludes women with previously demonstrated hypersensitivity to any components of tenofovir 1% gel.

This LoA reflects a change in the product packaging and change in the product manufacturer of tenofovir 1% gel.

This LoA clarifies the nature of the tenofovir levels outlined in the Study Procedures Section. Blood, not plasma, levels of tenofovir will be measured.

This LoA modifies data collection methods for neonatal hospital course and outcomes. Neonatal chart abstraction is now included specifically in the study procedures and sample informed consent form. The MTN-002 Protocol Team planned to collect data on neonatal hospital course and outcomes via maternal reports, verbal reports from neonatal providers, and maternal chart abstraction. The inclusion of neonatal chart abstraction allows for a more complete assessment of neonatal hospital course and outcomes.

Implementation

This LoA is official MTN-002 protocol documentation. Prior to implementing the revisions listed below, the MTN-002 study site 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.

Detailed modifications of the protocol text are indicated by ~~strikethrough~~ (for deletions) and **bold** for additions.

Detailed Listing of Revisions

1. In Section 5.3 Exclusion Criterion (added):

12. Previously demonstrated hypersensitivity to any components of tenofovir 1% gel

2. In Section 6.2 Administration, first sentence (added): Four grams of tenofovir 1% gel will be administered vaginally, using the **pre-filled** vaginal applicator provided, by the authorized clinician, approximately two hours prior to the expected time of cesarean section (optimally at least one hour prior to the collection of cord blood).

3. In Section 6.3 Study Product Formulation and Preparation, first paragraph, first through third sentences (added and deleted): Tenofovir gel is a clear, transparent viscous gel **provided in pre-filled vaginal applicators.** ~~packaged in epoxy inner-lined aluminum tubes with white polyethylene screw caps equipped with a puncture tip.~~ Each single-dose **vaginal applicator** ~~tube contains~~ **will deliver 4 grams of** ~~nominally 6 grams of~~ tenofovir gel at a concentration of 1% (weight per weight)**.** **The product is** formulated in purified water with edetate disodium, citric acid, glycerin, methylparaben, propylparaben, and hydroxyethylcellulose, with pH adjusted between 4.0 and 5.0. ~~The study gel is applied with a polyethylene applicator capable of administering a 4 gram dose.~~

4. In Section 6.3 Study Product Formulation and Preparation, second paragraph (deleted): ~~Immediately prior to application, the authorized clinician will fill the vaginal applicator by removing the cap from the tube of study gel, puncturing the metal seal on the tube with the pointed tip of the cap, screwing the end of the applicator onto the tube and slowly squeezing gel out of the tube and into the applicator. The plunger will stop when the applicator is full (contains the 4 grams of study product).~~

5. In Section 6.4.1 Study Product Supply, second sentence (deleted and added): Tenofovir 1% gel is manufactured, packaged, labeled, analyzed and released by ~~Gilead Sciences (Foster City, CA) under~~ **DPT Laboratories (San Antonio, TX) in accordance with** current good manufacturing practices (cGMP), 21 Code of Federal Regulations, conditions.

6. In Section 6.4.2 Study Product Acquisition, first sentence (added and deleted): Tenofovir 1% gel **in pre-filled** ~~and~~ vaginal applicators will be available through the DAIDS Clinical Research Products Management Center.

7. In Section 6.4.3 Dispensing, first sentence (added and deleted): The tenofovir 1% gel **in pre-filled** ~~tube for a study participant and a~~ vaginal applicator**s** will be dispensed only upon receipt of a written prescription from an authorized prescriber.

8. In Section 6.4.5 Retrieval of Unused Study Products, first sentence (deleted): Physician investigators and authorized study site staff must return any

unused **applicators containing tenofovir 1% gel** ~~study product tubes and unadministered study product in applicators~~ to the pharmacy.

9. In Section 7.3 Pharmacokinetic Measures, Table 3: Pharmacokinetic Measures: Gel Administration Day (Day 0), Pre-Gel Lab Component, second bullet, first sub-bullet (added and deleted): maternal **blood** ~~plasma~~ tenofovir level.

10. In Section 7.3 Pharmacokinetic Measures, Table 3: Pharmacokinetic Measures: Gel Administration Day (Day 0), Post-Gel Lab Component, second bullet (added and deleted): Draw blood for maternal **blood** ~~plasma~~ tenofovir level.

11. In Section 7.4 24 Hour Evaluation, Table 4: 24 Hour Evaluation, Laboratory Component, first bullet (added and deleted): Draw blood for maternal **blood** ~~plasma~~ tenofovir level.

12. In Section 7.4 24 Hour Evaluation, following Table 4 (added): **Infant chart review and abstraction of any neonatal adverse events noted therein will occur for the period of neonatal inpatient admission.**

13. In Section 7.6 Unscheduled Visit, Table 6: Unscheduled Visits, Laboratory Component, ninth bullet (added and deleted): *Maternal **blood** ~~plasma~~ tenofovir level.

14. In Section 7.9.2 Network Laboratory, fifth paragraph, first sentence and second sentence (added and deleted): As stated above, a validated assay for tenofovir in **blood** ~~plasma~~ is currently available. Validated assays for tenofovir in endometrial tissue, amniotic fluid and placental tissue have not yet been developed, but are expected to be ready in 200**8**~~7~~.

15. In Section 7.9.2 Network Laboratory, last paragraph, first sentence (added and deleted): **Blood** ~~Plasma~~ will also be analyzed for routine pharmacokinetic parameters (C_{max}, T_{max}).

16. In Section 8.3.1 Adverse Events, third paragraph, first sentence (added): Study site staff will document on study CRFs all AEs reported by or observed in study participants from the time of enrollment until study termination, **as well as AEs identified via infant chart review for the infant's inpatient admission period(s),** regardless of severity and presumed relationship to study product.

17. In Section 10.3 Study Hypothesis, first bullet (added and deleted): Study hypothesis 1: **Blood** ~~Plasma~~ absorption in participants will be detectable in a percentage of women similar to that seen in HPTN 050 (approximately 33%).

18. In Section 10.4 Sample Size, first paragraph, first sentence (added and deleted): The power of the study can be characterized as follows: if the overall absorption rate (defined as the proportion of women with detectable levels of PMPA in **blood** ~~plasma~~, endometrium, cord blood, placental tissue, and/or amniotic fluid) was expected to be 33%, 16 women would provide 72% power to exclude absorption rate > 60%.

19. In Section 10.6.2 Primary Analysis, first paragraph, second sentence (added and deleted): Similarly, descriptive statistics for continuous variables will be used to describe levels of tenofovir in levels in **blood** ~~plasma~~, in endometrium, in cord blood, in placental tissue, and in amniotic fluid.

20. In Section 10.6.2 Primary Analysis, second paragraph, first sentence and fifth sentence (deleted): Blood ~~plasma~~ pharmacokinetics of tenofovir will be evaluated after vaginal administration.

    The ratio of concentrations of tenofovir in maternal blood relative to temporally matched cord blood, amniotic fluid, and endometrial tissue concentrations, and ratio of maternal blood ~~plasma~~ relative to intracellular peripheral blood mononuclear cell (PBMC) tenofovir and tenofovir diphosphate levels will be calculated and summarized using descriptive statistics.

21. In Section 13.3.1 Risks, seventh paragraph, first sentence (added and deleted): This is a single-dose study and maternal **blood** ~~plasma~~ levels are expected to be inconsistent and low-level, if detected.

22. In Appendix 1, Laboratory Section, fourteenth item (added and deleted): Maternal **Blood** ~~Plasma~~ Tenofovir Level.

23. In Appendix VI: Sample Informed Consent Form (Screening and Enrollment), What Do I Have to Do If I Am In This Study Section, ninth sentence (added): We will also ask you to sign permission forms so that we can get copies of any hospital records **for you and your baby** for the time that you are in the study.

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