

**LETTER OF AMENDMENT #01 TO:**

**MTN-003**

**DAIDS Document ID 10622**

**Phase 2B Safety and Effectiveness Study of Tenofovir 1% Gel, Tenofovir Disoproxil Fumarate Tablet and Emtricitabine/Tenofovir Disoproxil Fumarate Tablet for the Prevention of HIV Infection in Women**

**Version 2.0/31 December 2010**

**IND # 55,690**

**Letter of Amendment Date: April 5, 2011**

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**Instructions to Study Sites from the Division of AIDS**

The following information impacts the MTN-003 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. This must be approved by your IRBs/EC before implementation. The following information also impacts the Sample Informed Consent for Enrollment. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment (LoA).

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**Summary of Revisions and Rationale**

This LoA does not impact the overall design and study visit schedule for MTN-003. The primary reason for this LoA is to institute the collection of Peripheral Blood Mononuclear Cells (PBMCs) for pharmacokinetic (PK) analysis at selected sites. This LoA provides for modification to the protocol regarding the following items:

1. Study background, regarding the rationale for collection of PBMC archive for PK
2. Study procedures, regarding the schedule of collection for PBMC archive
3. The Sample Informed Consent for Enrollment, to update the total projected duration of the study from 36 to 38 months, and to provide sample language for a supplemental information sheet to explain the purpose, nature and schedule of PBMC collection to VOICE participants
4. Communication with DAIDS Medical Officer regarding study drug supply

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**Implementation**

Upon receiving final IRB/EC and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Except for modifications to the Protocol Team Roster, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

## Detailed Listing of Revisions

1. In Section 2, INTRODUCTION, the following text is added to Section 2.10.2, Rationale for Study Design, at the end of the subsection, Pharmacokinetics:

The extent to which ARV-based PrEP provides protection from infection with HIV is directly related to the ability of the ARV to be present in fully activated form in the cells that comprise the principal target for infection. This observation provides the rationale for evaluating daily dosing of ARVs delivered either systemically (orally) or topically (vaginally) in the VOICE Study. However, results from the iPrEx study, which assessed effectiveness of oral FTC/TDF prescribed daily to MSM as PrEP, indicated that these ARVs were detectable in only half of the participants assigned to the active product arm, indicating relatively poor adherence to the assigned regimen.<sup>11</sup> Importantly, the iPrEx study used two critical measures to determine whether participants were taking the active study product. First, as is scheduled in VOICE, iPrEx used an assay to detect TFV levels in plasma obtained at quarterly visits. Plasma levels of tenofovir may be detectable less than one hour after initiating oral ingestion, typically reaching  $C_{max}$  approximately 1 – 2 hours after a 300 mg dose, depending on whether drug is administered with food. TFV levels reach a steady state after approximately 1 – 2 days at the dose prescribed (personal communication, Craig Hendrix). Thus, a limitation of using plasma tenofovir levels to determine adherence is that they reflect only recent product use. This raises the potential for participants who have not been routinely adherent to study product over the course of study participation to have apparently appropriate plasma levels of TFV simply by taking the drug for several days prior to sampling. Thus, objective measures of adherence to study product over the longer term are needed.

The second assay used by the iPrEx team, and being performed in other large studies of ARV PrEP including the Partners PrEP Study assessing ARV PrEP in HIV-discordant couples in Kenya and Uganda, was measurement of TFV-DP in PBMC. In contrast to plasma TFV levels, TFV-DP levels in PBMC reflect relatively long-term ingestion of TDF/FTC or TDF on its own. Thus, this measurement reflects accumulation of TDF over a longer timeframe, and thus is presumably more reflective of sustained adherence to study product. In iPrEx, in a small case-control analysis of participants who acquired HIV vs. those who did not, TFV-DP levels in PBMC were highly inversely correlated with likelihood of HIV acquisition. MTN-001, a study that assessed TFV-DP levels in various compartments after sustained oral, vaginal, and combined oral and vaginal dosing of tenofovir, demonstrated that TFV-DP was infrequently detected in PBMC among women using only vaginal TFV gel. However, as more sensitive assays for TFV-DP and related metabolites (TFV-MP) are developed, it is likely that drug may be detectable in PBMCs in women on vaginal gel product, which could provide an additional biomarker of adherence. CAPRISA 004, which demonstrated significant protection from HIV acquisition by coitally dependent vaginal use of 1% tenofovir gel also showed that higher rates of adherence to product use, as estimated by count of used applicators, was significantly associated with the level of protection. The results of iPrEx and CAPRISA 004 both support the collection of data other than participant self-report as a critical strategy for understanding the relationship between product adherence and effectiveness. VOICE will collect and preserve PBMC at sites with capacity in participants on both the oral and gel arms in VOICE, for future assays of TFV-DP and FTC-TP. Sites must be approved by the MTN Network Laboratory.

2. In Section 7, STUDY PROCEDURES, PBMC archive is added to the end of Section 7.5.3, Laboratory Procedures, the very end of Section 7.6.1, Participants Who Become Infected with HIV, and Section 7.11, Laboratory Evaluations.

### 7.5.3 Laboratory Procedures

- **PBMC archive (for consenting participants at selected sites approved by NL)**
  - **At the first quarterly visit following consent and every six months thereafter, during scheduled study participation**
  - **As indicated in Section 7.6.1**

### 7.6.1 Participants Who Become Infected with HIV

**Upon documentation of two positive rapid HIV tests during a follow-up visit, participants who have provided consent for PBMC collection will have blood collected for this purpose (at sites with NL approval). Sample 2 may be collected at the time of specimen collection for PBMC archive with NL approval.**

### 7.11 Laboratory Evaluations

#### Local, Regional, or Network Laboratory

The location of laboratory evaluations will depend on laboratory capacity.

- Urine pregnancy test
- Dipstick urinalysis
- HIV serology
- Syphilis serology
- Complete blood count with platelets, WBC, and differential
  - Hemoglobin
  - Hematocrit
  - Mean corpuscular volume
  - Platelets
  - White blood cells
    - Absolute neutrophil count
    - Percent neutrophils
    - Absolute lymphocyte count
    - Absolute monocyte count
    - Absolute eosinophil count
    - Absolute basophil count
- Serum chemistries
  - ALT
  - AST
  - Creatinine
  - Phosphate
- Trichomonas rapid test
- BV rapid test
- Vaginal pH

- Wet mount (KOH) for candidiasis
- Pap smear interpretation
- Plasma archive
- HIV-1 RNA PCR
- CD4+ T Cell Count
- Urine SDA for chlamydia and gonorrhea
- HBsAg
- HBsAb
- HSV-1 antibody
- HSV-2 antibody
- **PBMC archive (at sites with NL approval)**

#### Network Laboratories

- Gram stain assessment of vaginal fluid slides
- Biomarker analyses of vaginal swabs
- Biomarker analyses of endocervical swabs
- Standardized and sensitive HIV-1 resistance tests
- Blood TDF level
- Blood FTC level
- **Intracellular TFV-DP and FTC-TP**

The following table was added to Appendix I to summarize the specimen collection and laboratory assay schedule for the PBMC archive.

#### SCHEDULE OF PBMC COLLECTION

	First QRT	Q 6 Months	INT
<b>PBMC Collection at Sites with NL Approval</b>	X*	X	▲
<b>TFV-DP and FTC-TP Levels</b>	X*	X	▲

\*Applies to the participant's first QRT visit following consent for PBMC collection, then every six months thereafter during study participation.

▲ If a scheduled collection is missed, PBMC should be collected at the next completed visit (scheduled or interim), unless the next visit is less than 4 weeks away from the next scheduled PBMC collection, (in which case collection could occur at the latter visit). Participants who are temporarily held or permanently discontinued from study product should continue to have scheduled PBMC collection unless otherwise specified in the MTN-003 SSP Manual.

3. In APPENDIX VI, the Sample Informed Consent for Enrollment is modified to include an update to the duration of follow-up and an explanation of the purpose, procedures and schedule for collection of blood for PBMCs, as well as a check box and signature line. The modification to the informed consent document regarding the PBMC archive will only be adopted at network-approved sites with capacity for PBMC collection and NL approval.

Text was modified under STUDY PROCEDURES, fourth paragraph, first sentence.

If you decide to enroll in the study, after today you will be in the study from 14 to 3638 months, depending on when you join.

At approved sites, the following sample text may be employed for use in a supplemental information sheet regarding the collection of blood for PBMC archive.

**Tenofovir and Truvada, like all medications, go through changes after they go into the body. Tenofovir and Truvada need to go through changes in the blood to fight against HIV. We would like to do a test for this in the blood of VOICE participants now and every six months until the end of VOICE. We would also like to do this test for anyone who becomes infected with HIV during VOICE. This kind of test is done on a part of the blood called PBMC. Because we will not know until the end of VOICE which participants are taking active tablets and gel and which are taking placebo tablets and gel, we need to collect blood from everyone while VOICE is ongoing. You will give [xx mL [or local equivalent] of blood from your arm] for this test. As much as possible, we will get this blood at times you are already having your blood taken for other reasons in VOICE. With blood draw, there is always a small risk of extra bleeding, pain, feeling dizzy, or having a bruise, small clot or infection where the needle goes into your arm. You may get no direct benefit from consenting to this testing, but you may get some personal satisfaction from being part of research on HIV prevention.**

The researchers do not plan to contact you or your doctor with any results from tests done on PBMC. This is because these kinds of test results are not used to manage a person's health. The results of these tests will be important for helping researchers understand the results of VOICE. You do not need to do this test to stay in the study, or to find out if you received active or placebo study products in VOICE. We will tell you more about what information you will receive at the end of VOICE, if you request this.

I agree to allow my blood to be collected for PBMC testing.

OR

I do not agree to allow my blood to be collected for PBMC testing.

\_\_\_\_\_  
Participant Name  
(print)

\_\_\_\_\_  
Participant Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Study Staff Conducting  
Consent Discussion (print)

\_\_\_\_\_  
Study Staff Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
Witness Name  
(print)

\_\_\_\_\_  
Witness Signature

\_\_\_\_\_  
Date

4. In Section 6, STUDY PRODUCT, a modification is made to language in Section 6.5, Study Product Dispensing, second paragraph, first sentence, to trigger consultation with a DAIDS Medical Officer for any study product supply greater than two months.

If a participant will miss two or more consecutive visits (~~requires more than a 60-day supply of study product~~), approval from a DAIDS Medical Officer must be obtained prior to dispensing any study product(s).

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