LETTER OF AMENDMENT #02 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: August 19, 2011

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 IRB/EC before implementation. The following information may also impact the Sample Informed Consent. Your IRB/EC will be responsible for determining the process of informing subjects of the contents of this Letter of Amendment.

Summary of Revisions and Rationale

This LoA does not impact the overall design and study visit schedule for MTN-003. The primary reasons for this LoA are to update the study background regarding outcomes of other HIV prevention trials and to institute the collection of hair for pharmacokinetic (PK) analysis at sites approved by the Network Laboratory (NL). This LoA provides for modification to the protocol regarding the following items:

1. New information regarding recently released results of three HIV prevention trials, and the rationale for continuing all five arms of VOICE as originally designed
2. Update to the expected timeline for the collection of unused study product following PUEV
3. Collection of hair for PK analysis, with updates to several sections
    a. INTRODUCTION, regarding rationale for PK analysis of hair;
    b. STUDY PROCEDURES and APPENDIX I, regarding the schedule of collection for hair specimens and laboratory assays;
    c. APPENDICES, to add a new Sample Informed Consent for collection of hair for PK analysis.

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 2.8.3, Clinical Studies of Emtricitabine and Tenofovir Disoproxil Fumarate in Combination (Truvada®), at the end of the subsection, Effectiveness as PrEP:

FEM-PrEP

The FEM-PrEP Study is a Phase 3, randomized, placebo-controlled trial of the effectiveness of daily oral FTC/TDF for HIV prevention among HIV-uninfected women in Kenya, South Africa and Tanzania. The FEM-PrEP study enrolled HIV-negative women between the ages of 18 and 35 who were at higher risk for HIV. Higher risk was defined as: 1) has had at least one vaginal sex act in the last two weeks, or 2) has had more than one sexual partner in the last month. Only women who used study-approved contraception at enrollment were eligible for participation. The study was conducted at four sites in three countries (Bondo, Kenya; Bloemfontein and Pretoria, South Africa; and Arusha, Tanzania). All participants in the study were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. This trial was designed to close at 72 HIV endpoints. However, at the time of a scheduled review by the trial's Independent Data Monitoring Committee on April 7, 2011, 56 HIV endpoints had occurred, with 28 endpoints in the FTC/TDF arm and 28 endpoints in the placebo arm; the trial was therefore stopped early due to futility. No significant safety concerns were noted. Pregnancy rates were noted to be higher in women taking hormonal contraceptives (at the onset of participation) and FTC/TDF compared with those taking hormonal contraceptives and the placebo. Final study results are expected to be available in late 2011 or early 2012.

Immediately following the public release of this information, the FEM-PrEP outcome was shared with the VOICE study team; materials to inform site IRBs/ECs and study participants were also provided. The FEM-PrEP outcome was considered during a scheduled interim review of VOICE study data on May 9, 2011 by the NIAID Prevention Trials Data and Safety Monitoring Board (DSMB), which oversees the conduct of VOICE. The VOICE DSMB recommended that all five arms of VOICE continue as originally designed. The written report from this review was shared with the VOICE study team and site IRBs/ECs.

Partners PrEP

The Partners PrEP Study is a double-blind, placebo-controlled, Phase 3 clinical trial to assess the safety and efficacy of daily oral PrEP for the prevention of HIV infection within heterosexual African HIV serodiscordant couples, using TDF alone or in the fixed dose combination of FTC/TDF. The Partners PrEP Study enrolled 4,758 HIV serodiscordant couples from 9 clinical trial sites in Kenya and Uganda. HIV-uninfected partners were randomly assigned in equal numbers to one of three study groups (TDF tablet, FTC/TDF tablet, and placebo tablet). Of the HIV-uninfected partners at enrollment, 38% were women. The study began in July 2008 and enrollment was completed in November 2010. All study participants received a comprehensive package of HIV prevention services, which included intensive safer sex counseling (both individually and as a couple), HIV testing, free condoms, testing and treatment for sexually transmitted infections, and monitoring and care for HIV infection. The Partners PrEP Study DSMB at its 10 July 2011

meeting reviewed data collected through 31 May 2011. Through that date, a total of 78 HIV infections occurred in the study: 18 among those assigned TDF, 13 among those assigned FTC/TDF, and 47 among those assigned placebo. Those who received TDF had an average of 62% fewer HIV infections (95% CI 34-78%, P = 0.0003) and those who received FTC/TDF had 73% fewer HIV infections (95% CI 49-85%, P <0.0001) than those who received placebo. Subgroup analysis by gender showed that both TDF and FTC/TDF significantly reduced HIV risk in both men and women within serodiscordant partnerships. For TDF, the HIV risk reduction was 68% for women (95% CI 29-85%, P = 0.01) and 55% for men (95% CI 4-79%, P = 0.04). For FTC/TDF, the HIV risk reduction was 62% for women (95% CI 19-82%, P = 0.01) and 83% for men (95% CI 49-94%, P = 0.001). Among 42 total HIV infections in women, 8 were in the TDF arm, 9 were in the FTC/TDF arm, and 25 were in the placebo arm. The rate of serious medical events was similar for those assigned to TDF, FTC/TDF, or placebo. Adherence to study drug was very high, with greater than 97% of dispensed doses of study drugs taken, according to self-report and pill counts. More than 95% of participants were retained in follow-up. Given the efficacy results, the Partners PrEP DSMB recommended that administration of placebo be suspended; participants initially randomized to TDF and FTC/TDF will remain on those medications, and those initially randomized to placebo will start receiving TDF or FTC/TDF via random assignment.

TDF2

The TDF2 Study is a Phase 2B study that assessed the safety, adherence and efficacy of daily oral FTC/TDF in 1,200 HIV-uninfected heterosexual male and female participants aged 18-39. The trial, originally known as the Botswana PrEP Study, began in 2005 as a Phase III trial of TDF. In 2007, the study product was changed to FTC/TDF. In 2009, the study completed enrollment of 1,200 participants, but due to lower than expected HIV incidence in the study and suboptimal retention, it was determined that the study at this sample size would not be able to evaluate its primary objective of efficacy. The trial continued, but with an intent to evaluate safety and adherence only. Of the 1,200 participants in the TDF2 Study, 45% of whom were women, 601 were randomly assigned to FTC/TDF, and 599 were assigned to placebo. All participants were provided comprehensive HIV prevention services, including male and female condoms, intensive risk-reduction behavioral counseling, and testing and treatment for sexually transmitted infections. During the study, 33 of 1,200 participants acquired HIV (nine of the 601 participants on the FTC/TDF arm and 24 participants of the 599 on the placebo arm), corresponding to a 62.6% reduction in HIV acquisition for those assigned to FTC/TDF, compared to placebo (HR 0.37, 95% CI 21.5-83.4, P = 0.013). Among 21 total HIV endpoints among women in the trial, 7 were in the FTC/TDF arm and 14 were in the placebo arm. While results for the subset of women in the trial did not meet statistical significance (HR 0.51, 95% CI -0.217-80.8, P = 0.107), a non-ITT analysis among women thought to have a supply of study drug (3 HIV endpoints in the FTC/TDF arm and 13 in the placebo arm) found an estimated efficacy of 75.5%, P = 0.021. No significant safety concerns were noted, though participants randomized to the FTC/TDF arm did experience more nausea, vomiting, and dizziness than those randomized to placebo.

Immediately following the public release of this information, the results of Partners PrEP and TDF2 were shared with the VOICE study team. Materials to inform site IRBs/ECs and study participants of the trial results were also provided. The results of Partners PrEP and TDF2 were reviewed by the NIAID Prevention Trials DSMB charged with monitoring VOICE on July 18, 2011. After careful consideration, the VOICE DSMB decided to move

the next routinely scheduled safety and efficacy review of VOICE from November 2011 to mid-September 2011.

Justification for VOICE in Light of Recent Findings

Analysis by the VOICE team, as well as consultation with experts in bioethics at the U.S. National Institutes of Health, has concluded that there is justification to continue all five arms of VOICE as currently designed. The CAPRISA 004, iPrEx, FEM-PrEP, Partners PrEP, and TDF2 studies have all provided data to help answer the question of whether topical and oral formulations of tenofovir are effective for preventing HIV in HIV-uninfected men and women. However, VOICE is positioned to help resolve the conflicting results from FEM-PrEP and Partners PrEP/TDF2 described above and to address unanswered questions that will be critically important for future rollout of PrEP for women. Most importantly, the currently available data do not conclusively answer the question of whether oral PrEP is an effective HIV prevention strategy for women. FEM-PrEP has approximately the same number of HIV endpoints among women as TDF2 and Partners PrEP combined. Thus, the results to date for studies which have enrolled women are fairly evenly split between showing efficacy (within TDF2 and Partners PrEP) and showing no difference (within FEM-PrEP) between placebo and oral FTC/TDF. Because women are biologically different from men in ways very relevant to HIV transmission, it is critically important to determine whether oral PrEP is effective in women. The population of women enrolled in VOICE differs from the populations in these other studies in that VOICE participants are diverse in terms of their risk factors for HIV acquisition, and are not all in HIV-serodiscordant couples. The adherence data from VOICE may help to elucidate why FEM-PrEP results were different from results in TDF2 and Partners PrEP. VOICE is collecting not only pill counts and self-reports, but will also conduct PK testing on hair, plasma and PBMCs as independent measures of adherence. VOICE is also gathering data on important secondary endpoints including the risk of developing resistance while taking PrEP, the potential impact on HSV-2 transmission, and whether there is a difference between TDF and FTC/TDF in preventing HIV acquisition and in the HIV resistance mutations seen among seroconverters during the study. Given that PrEP will likely be offered to healthy HIV-uninfected individuals and has potential side effects and financial costs, decisions about licensure and roll-out will require clear evidence of effectiveness and information on the risk-benefit ratios in specific populations. Discontinuing VOICE or changing the design such that the major questions about effectiveness of the interventions cannot be resolved also obviates the contributions made by the women enrolled in VOICE to date. Since it is not yet clear whether oral PrEP is an effective intervention for prevention of HIV infection in women, the VOICE study team and the DSMB will continue to evaluate the scientific necessity of including placebo to answer the primary question and to resolve questions regarding conflicting data presented by other trials. The DSMB is best positioned to consider whether the results of these PrEP trials, alone or in combination with available interim data from VOICE, suggest that the placebo arm should be stopped. The VOICE team has worked to minimize risks to participants by providing safer sex counseling, HIV testing, condoms, and treatment of STIs to participants. Importantly, VOICE is not denying participants in the placebo arm access to something they would otherwise receive, because neither oral PrEP nor microbicides are currently available in VOICE site countries.

2. In Section 6.6, Retrieval of Unused Study Products, fifth paragraph, the second sentence is modified as follows:

If the participant does not bring her remaining supplies to the PUEV, study staff must arrange to retrieve the supplies within ~~2~~**7** business days.

3. 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:

A secondary objective of VOICE is to evaluate the pharmacodynamic relationship between plasma drug concentrations and study outcomes. The VOICE study was recently amended (in LoA #01 to Version 2.0) to include collection of PBMCs for pharmacokinetic analysis, reflecting the substantial value of intracellular drug levels as an objective measure of adherence to study product over a longer time period than is afforded with plasma levels of drug. While VOICE will have multiple self-reported measures of adherence to inform understanding of safety and efficacy outcomes as they relate to actual product use, objective measures of adherence will be critical, as self-reported adherence measures do not consistently reflect physiologic drug levels or inter-individual variation in PK.

A research group at the University of California at San Francisco (UCSF) has developed expertise in monitoring ARV adherence and exposure by measuring ARV concentrations in small samples of hair. Because the concentration of drugs in hair reflects uptake from the systemic circulation over an extended time window (weeks to months), hair analysis provides a reliable measure of exposure to these medications over time. These investigators have demonstrated that hair concentrations of protease inhibitors and NNRTIs are directly related to the likelihood of virologic suppression as measured by plasma HIV-1 viral load in participants in the Women's Interagency HIV Study (WIHS). In these analyses, hair concentrations of drug are stronger independent predictors of successful ART than self-reported adherence measures, age, race, initial viral load and CD4 T-cell counts, and degree of prior ARV experience. Hair drug concentrations have been used as a biomarker for adherence and exposure in a variety of research settings around the world, including in HIV-infected women and their children in Uganda, HIV-infected pregnant women in South Africa, and HIV uninfected participants in the Global iPrEx PrEP trial. Good acceptability rates for collection of small hair samples were noted in the iPrEx PrEP trial for the measurement of tenofovir and FTC concentrations in hair.

VOICE will collect hair for PK assays at sites with capacity for participants who provide a separate consent for this procedure. Sites must be approved by the MTN Network Laboratory. Participants will not be required to take part in hair collection for PK analysis to continue participation in VOICE. Sites are encouraged to consult their Community Advisory Boards and engage community education staff in their efforts to understand and address potential challenges related to collection of small hair samples for PK analysis. Hair samples will be analyzed for drug concentrations at the end of the study and then all remaining hair samples will be destroyed.

4. In Section 7, STUDY PROCEDURES, hair collection for PK is added via supplemental text at the end of Section 7.5.1, Administrative, Behavioral, and Regulatory Procedures, Section 7.5.2, Clinical Procedures, Section 7.5.3, Laboratory Procedures, Section 7.6.1, Participants Who Become Infected with HIV, Section 7.11, Laboratory Evaluations, and via a table added to the end of APPENDIX I.

7.5.1 Administrative, Behavioral, and Regulatory Procedures

- **Informed consent for hair collection for PK analysis (at sites approved by NL) (APPENDIX VIII)**

7.5.2 Clinical Procedures

- **Hair collection (for consenting participants at sites approved by NL)**
  - **At first Monthly Visit following regulatory approval**
  - **Every other month prior to PUEV**
  - **At PUEV**
  - **If indicated**

Note: Hair samples will be collected on all participants who provide separate informed consent for this collection, beginning at the first monthly visit following regulatory approval, once consent is obtained (or as soon as possible thereafter).

Note: If a scheduled collection other than PUEV is missed, hair should be collected at the next visit. Participants who are temporarily held or permanently discontinued from study product should continue to have scheduled hair collection unless otherwise specified in the MTN-003 SSP Manual.

7.5.3 Laboratory Procedures

- **Hair testing for PK, at sites approved by NL**

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 hair collection will have small samples of hair collected for PK analysis (at sites approved by NL) at that visit. Hair for PK analysis will be collected on the same day as the two positive rapid tests, or at a later time as soon as possible thereafter, as determined by the IoR/designee. Hair collection for PK will discontinue for these participants after this visit.

7.11 Laboratory Evaluations

UCSF/Gandhi Laboratory

- **Hair TFV level**
- **Hair FTC level**

A new table was added following APPENDIX I to summarize the collection and laboratory assay schedule for hair specimens.

SCHEDULE OF HAIR COLLECTION AND PK ASSAYS

	1ST MONTHLY VISIT FOLLOWING REGULATORY APPROVAL	EVERY 2 MONTHS PRIOR TO PUEV	INT	PUEV	IF 2 POSITIVE HIV RAPID TESTS NOTED AT FOLLOW-UP VISIT
Informed Consent for Hair Collection for PK Analysis	**X**				
Hair Collection	**X**	**X**	**▲**	**X**	**X**
Hair TFV and FTC Levels	**X**	**X**	**▲**	**X**	**X**

▲If a scheduled collection other than PUEV is missed, hair should be collected at the next visit. Participants who are temporarily held or permanently discontinued from study product should continue to have scheduled hair collection unless otherwise specified in the MTN-003 SSP Manual.

A supplemental Sample Informed Consent Document is added to the protocol as Appendix VIII.

SAMPLE INFORMED CONSENT (Hair Collection)
DIVISION OF AIDS, NIAID, NIH

MTN-003/VOICE

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

[SITE TO INSERT DATE]

PRINCIPAL INVESTIGATOR: [insert name]
PHONE: [insert number]
Short Title for the Study: VOICE

INTRODUCTION: You are taking part in the VOICE research study. As part of VOICE, you have blood drawn to check the amount of study product in your blood, and talk with staff about study product use. We are now asking for your permission to cut a small sample of hair from your head to check the amount of study product in this hair sample. Medicines go into many places in the body, including the hair. The amount of study product found inside the hair may provide a better idea of how much study product could be in the body after a long period of time. Hair sample testing has been part of other studies, and is being added to VOICE as another possible way to help researchers understand how much study product is needed to prevent HIV infection. This collection of the small hair sample is voluntary. You will be asked to sign or make your mark on this form to indicate whether you agree to have hair collected. You will be offered a copy of this form to keep. If you do not agree to have hair collected, or you change your mind later, you can still stay in VOICE.

WHAT WILL HAPPEN IF I AGREE TO THIS PART OF THE VOICE STUDY?

Every other study visit (once every 2 months), a trained study staff member will cut a total of about 100 hairs from the back of your head. Humans normally lose about 100 hairs from their head every day (mostly without realizing it). Removing this amount of hair should not disrupt your hairstyle and will not affect the normal new growth of your hair. This hair collection may continue until the end of your study participation (even if the study doctor temporarily or permanently stops your study drug), unless you become infected with HIV or decide you no longer want hair to be collected. If you become infected with HIV, we will collect the hair at the time that you test positive for HIV, then your hair will no longer be collected.

WHAT WILL BE DONE WITH THE HAIR?

We will keep your hair in a secure location here at the clinic until we send it to be tested by researchers at a laboratory in the US. All of the hair collected will be used for this testing. Once the hair is tested, the entire hair sample will be completely destroyed. Your hair samples will not be used for any other purpose. Study staff here will not see test results while VOICE is ongoing.

WHAT ARE THE RISKS?

There is a very small risk that the study staff may accidentally cut your skin or disturb your hair style when collecting the hair sample.

WHAT ARE THE BENEFITS?

You may get no direct benefit from consenting to this hair collection. You may feel personal satisfaction from being a part of this research. The results of these tests will be important for

helping researchers understand the results of VOICE. The researchers do not plan to contact you or your doctor with any results from tests done on your hair sample. This is because these kinds of test results are not used to manage a person's health.

WHAT ABOUT CONFIDENTIALITY?

The staff will follow the same steps to ensure your privacy as was explained in the enrollment informed consent for VOICE. Efforts will be made to keep your personal information confidential. Your name and other personal information will be protected by the research clinic staff. To keep your information private, hair samples will be labeled with your study identification number rather than your name. However, it is not always possible to guarantee confidentiality.

WHAT ARE MY RIGHTS?

Allowing study staff to collect hair samples is completely voluntary. If you decide not to have these hair samples collected, you can still stay in the VOICE study. If you decide now that you would like to have these hair samples collected, you may change your mind at any time. However, you must let us know that you no longer want these hair samples collected.

REIMBURSEMENT

You will receive [insert site-specific, IRB-approved, non-cash reimbursement strategies, e.g., hair ties, headwear, hair products, and/or vouchers for hair salon, etc.] for your time and effort.

WHAT DO I DO IF I HAVE QUESTIONS?

If you have questions about this test, or if you have a research-related injury, please contact [insert the name of the investigator] at [insert physical address and telephone number]. If you have questions about whom to contact at the research site, you should contact [insert name of the investigator or community educator or CAB member [staff will decide which] at [insert physical address and telephone number].

SIGNATURES

Please carefully read the statements below and think about your choice. No matter what you decide, it will not affect your participation in the VOICE study or your medical care. Please initial or mark your choice and sign or make your mark below.

[Insert signature blocks as required by the local IRB/EC, yes/no boxes may be used]

___ I agree to allow my hair to be collected for testing how much study product is found in the hair

OR

___ I do not agree to allow my hair to be collected for testing how much study product is found in the hair

_____	_____	_____
Participant Name (print)	Participant Signature	Date
_____	_____	_____
Study Staff Conducting Study Consent Discussion (print)	Staff Signature	Date
_____	_____	_____
Witness Name (print)	Witness Signature	Date

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