Letter of Amendment # 3 to:

HPTN 069: A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitibine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitibine (TDF+FTC) for Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women, Version 3.0, January 3, 2013, DAIDS Document ID: 11789
IND # 113,655

FINAL Version of LoA # 3: 5 March 2014

The following information impacts the HPTN 069 study and must be forwarded to all responsible Institutional Review Boards (IRBs) as soon as possible for their information and review. This Letter of Amendment must be approved by all responsible IRBs before implementation.

The following information impacts the sample informed consents. Your IRB will be responsible for determining the process of informing subjects of the contents of this letter of amendment (LoA).

Upon receiving final IRB 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 correspondence should be retained in the site's regulatory files.

If the HPTN 069 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.

Summary of Revisions and Rationale

1. Major Revisions 1-3

This Letter of Amendment clarifies that women who become pregnant on study can resume study product, at the discretion of the site investigator and in consultation with the PSRT, upon documentation of negative pregnancy and HIV testing.

All additions are in **bold** type and deletions are made with ~~strikethrough~~ type.

IMPLEMENTATION OF MAJOR REVISIONS

Major Revision 1 Section 6.6 – Pregnancy

Participants who **intend to or** become pregnant after study entry must discontinue study treatment immediately. ~~These p~~**P**articipants **who become pregnant** should be seen for a premature discontinuation evaluation within 7 days. These participants will continue to be followed off treatment, on study**, and will remain off treatment for the remainder of the study if they carry to term**~~until Week 49~~. **However,** p**articipants who have early termination of their pregnancy (intended or unintended) may resume study product, at the discretion of the site investigator and in consultation with the PSRT. In these cases, the participant must have a negative serum pregnancy test and a negative HIV test prior to resuming study product.** The PSRT must be notified of any pregnancies that occur in participants on study.

Major Revision 2 Appendix IV – Toxicity Management

The criteria for permanent discontinuation of study product use for an individual participant are:

- Study product-related toxicity requiring permanent discontinuation of study product per the guidelines above and below
- Completion of regimen as defined in the protocol
- Request by participant to terminate study product
- Clinical reasons determined by the Investigator
- Acquires HIV infection or hepatitis B virus (HBV) infection
- ~~Pregnancy~~

Any participant who prematurely discontinues study drug should be followed according to the procedures in the Schedule of Evaluations in Appendix I, with the exception of study drug dispensation, counseling, and adherence measurements.

Study drug will be temporarily withheld from a participant for any of the following reasons:

- Report of use of prohibited concomitant medications described in the SSP Manual. Study drug use may resume when the participant reports that he is no longer taking the prohibited medication, provided other reasons for temporary study drug hold/permanent discontinuation do not apply.

- The participant is unable or unwilling to comply with required study procedures such as HIV testing and routine laboratory assessments, or otherwise might be put at undue risk to their safety and well-being by continuing study drug use, according to the judgment of the Investigator. The Investigator must consult the PSRT on all temporary study drug holds instituted for this reason for further guidance on resuming study drug use, continuing the temporary hold, or progressing to permanent discontinuation. If study drug use is temporarily held/permanently discontinued for this reason, but the underlying reason for the temporary hold later resolves, the Investigator should consult the PSRT to resume study drug use at that time.

- The participant has one or more reactive HIV test results, or expresses a concern about having acute HIV infection. Criteria for resuming use of study drug in these circumstances are defined in the SSP.

- **The participant becomes pregnant and the pregnancy was terminated early (intended or unintended). Refer to Section 6.6 for instructions regarding the resumption of study product in the case of early termination of a pregnancy.**

Major Revision 3 Appendix V – Sample Screening and Enrollment Informed Consent Form

RISKS AND/OR DISCOMFORTS

Pregnancy

There are no adequate or well-controlled studies of pregnant women taking the medicines used in this study. If you are currently pregnant, you are not eligible to be in this study.

If you can get pregnant and are engaging in sexual activity that could lead to pregnancy, you must agree to use a form of contraception (condoms with or without a spermicidal agent; diaphragm or cervical cap with spermicide; IUD; Hormone-base contraceptive) during the trial and for 30 days after stopping the study medication.

If you become pregnant after joining the study, you will be asked to discontinue study treatment immediately. You will be asked to come to the clinic within 7 days of the site knowing of your pregnancy in order for the clinician to examine you. **If you carry your baby for the normal length of time, ~~Y~~y**ou will continue to be followed on study, but you will no longer take any study medicine. **If your pregnancy ends early (intended or unintended), you may be able to re-start study medicine, if your study clinician says it is okay to do so.**