

FINAL

Letter of Amendment # 1 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 # 1: May 24, 2013

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

Major Revisions

1. The background section of the protocol has been modified to include the recently released results of the VOICE study (MTN-003). The reference list has been updated as well. (Major Revision 4) This change is also reflected in Appendix V, the sample informed consent form (Major Revision 6a).
2. The inclusion criterion concerning the allowable calculated creatinine clearance value for entry into the study is revised for female participants to ≥ 60 mL/minute. This lower value is added so as not to unnecessarily exclude healthy women with normal renal function. The allowed value for men remains unchanged. This change is reflected in Section 3.1.
3. The allowable window to complete the Week 48 DXA scan is increased from -14 days/+14 days to -28 days/+28 days. This change allows for greater scheduling flexibility for sites and participants in order to ensure that a follow-up scan for a participant will be captured. This change is reflected in Section 5.5 and the Schedule of Evaluations (Major Revision 5).
4. The list of protocol references has been updated to reflect the addition of the VOICE results.

5. An update to Appendix I – Schedule of Evaluations, Footnote 7 – has been made per Major Revision number 3 above.
- 6a-b. Updates to Appendix V – Sample Screening and Enrollment Consent Form - have been made per Major Revision number 1 above to include VOICE results. In addition, FEM-PrEP results are also added as these were not previously outlined in the consent form. As a result of an update to the package insert for maraviroc (dated February 2013), the informed consent form has also been updated to include information related to possible severe skin and hypersensitivity reactions.
- 7a-e. Updates to Appendix VI and VII – Sample Informed Consent Form For Tissue Subset (Rectal Component) and Sample Informed Consent Form For Tissue Subset (Vaginal Component), respectively – have been made to clarify that sites may have slots available for both the main study and the main study plus the Tissue Subset, and that the sites will inform the participants of which slots are available so that they may choose which they want to participate in or decline participation if the choice they want is not available. This has been clarified because sites participating in the Tissue Subset have limited slots available for the main study only. Once those are full, the only option available to participants screening for the study would be to enroll in the Tissue Subset plus the main study. In addition, both consent forms have been fixed to remove the collection of rectal/vaginal fluid at enrollment, which is not required, to adding the collection of rectal/vaginal fluid at Weeks 24, 48, and 49 visits, where it is required.

Minor Revisions

1. The word “absolute” is removed from the second sub-bullet in Section 3.1 (laboratory values). It was a typographical error.
 2. The abbreviations for the liver function laboratory tests were transposed in Section 3.1. This has been corrected.
 3. In Section 3.6, sections cited for further reference concerning participant withdrawal and completion of a final evaluation are incorrect. The proper sections are now listed.
 - 4a-b. In Section 5.8, under “At Enrollment”, the word “only” has been added to the second bullet, and “cervical” is removed from the row of the Schedule of Evaluations concerning the collection of tissue for GALT T cell phenotyping. This testing is only being conducted in rectal tissue.
 5. The formula for calculating creatinine clearance in females is added to the Schedule of Evaluations, Footnote 10. Additionally, wording is added to the same Footnote to offer instructions to correctly record the creatinine clearance on the CRF.
 6. In Appendix IV, the formula for calculating the fractional excretion of phosphate is corrected to reflect that the plasma result used in the formula is for plasma creatinine.
 7. The word “do” was left out of the sentence in the informed consent which declines pharmacogenomic testing. Adding the word “do” into the sentence makes it grammatically correct, but does not change meaning of the sentence.
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All additions are in **bold** type and deletions are made with ~~striketrough~~ type.

IMPLEMENTATION OF MAJOR REVISIONS

Major Revision 1 Section 1.1.1 – Pre-Exposure Prophylaxis (PrEP), Paragraph 8

In contrast to the studies outlined above, the FEM-PrEP study was stopped early (April 2011) because the independent Data and Safety Monitoring Board (DSMB) determined that it was highly unlikely to demonstrate that use of TDF/FTC was efficacious in prevention of HIV in a study population of almost 2,000 African women; HIV incidence in the TDF/FTC group was 4.7 per 100 person-years and in the placebo group was 5.0 per 100 persons-years (P=0.81) ([Van Damme, Corneli et al. 2012](#)). A second study, MTN-003 (VOICE), was designed to compare the efficacy of daily 1% TFV gel, daily oral TFV, and daily oral TDF-FTC among heterosexual African women; both the daily oral TFV arm and the daily 1% TDF gel arms were stopped due to futility (September 2011 and November 2011 respectively) ([NIAID 2011](#); [NIAID 2011](#)). ~~The study has completed data collection and is in the process of~~ **Analysis of the data** assessing the impact of TDF-FTC on HIV acquisition **showed that too few women had used the gel or tablets to be able to tell whether they would work to prevent HIV infection. (Marrazzo et al) The VOICE results are consistent with FEM-PrEP results in that each study suffered low adherence to the study product, and** ~~The inconsistent PrEP results in women are presently unexplained and~~ support the need for continued work in this area to better understand causal factors in futility findings and to identify the potential value of alternative PrEP agents for women.

Major Revision 2 Section 3.1 – Inclusion Criteria, Seventh bullet, Fifth sub-bullet

- **For men, c**Calculated creatinine clearance ≥ 70 mL/minute using the Cockcroft-Gault equation; **for women, calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation**

Major Revision 3 Section 5.5 – Weeks 24 and 48 – Clinical Procedures, Fourth bullet

- DXA scan (Week 48 only). (The window for completing the DXA scan at this visit is ~~-1428~~ days/**+1428** days of the Week 48 visit. The other procedures completed at Week 48 will follow the standard allowable window.) DXA scan is only completed for participants who had a scan completed at enrollment.

Major Revision 4 Section 11 - References

MacInnes A, e. a. (2011). "Maraviroc can improve lipid profiles in dyslipidemic patients with HIV: results from the MERIT trial." [HIV Clinical Trials](#) 12(1): 24-36.

Marrazzo J, et al (2013). "Pre-exposure Prophylaxis for HIV in Women : Daily Oral Tenofovir, Oral tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN-003)." CROI 2013.

Martin, A., M. Bloch, et al. (2009). "Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-Lamivudine: a randomized, 96-week trial." Clin Infect Dis 49(10): 1591-1601.

Major Revision 5 Appendix I – Schedule of Evaluations and Procedures, Footnote 7

⁷Week 48 only. The window for completing the DXA scan at this visit is -1428 days/+1428 days of the Week 48 visit. The other procedures completed at Week 48 will follow the standard allowable window. Only participants that received a DXA scan at Enrollment will receive a scan at Week 48.

Major Revision 6a Appendix V – Sample Screening and Enrollment Informed Consent Form – Purpose of the Study – New Fourth Paragraph

Additionally, two studies showed support for the use of antiretrovirals for HIV prevention. The CDC TDF-2 trial showed that daily TDF/FTC was safe and effective for prevention of HIV infection among African heterosexual men and women compared to placebo. The Partners PrEP Study, which enrolled African heterosexual couples (one HIV positive and the other HIV negative), compared TDF once daily and TDF/FTC once daily regimens versus placebo. The TDF and TDF/FTC PrEP demonstrated a lower chance of getting HIV. Both studies showed that taking these drugs in this manner was safe and well-tolerated.

There were also two studies that had different results than those mentioned above. The FEM-PrEP study and the VOICE study (MTN-003) were designed to test if taking anti-HIV drugs could be used to prevent a person from getting HIV. These two studies involved the participation of African women only (about 2,000 in the FEM-PrEP study and about 5,000 in the VOICE study). The VOICE study, for example, tested whether vaginal gel or oral tablets could prevent HIV in African women, and whether they were safe. The women in VOICE were asked to take the gel or to take the tablets every day. The tablets used in VOICE contained two of the same drugs we use in this study (emtricitabine and tenofovir), but are in separate tablets for this study. The VOICE study had no safety concerns about the gel or the tablets used. However, neither of these studies (FEM-PrEP or VOICE) could determine if the anti-HIV drugs could be used for prevention of HIV because the researchers found that too few women had used the gel or tablets to be able to tell whether they would work to prevent HIV infection.

These studies show that it is important for participants to take their study medication as instructed by the study team so that we can answer the questions that we are asking in this study about the safety and tolerability of these drugs.

Major Revision 6b Appendix V – Sample Screening and Enrollment Informed Consent Form - Study Medications

The following serious side effects have been associated with the use of maraviroc:

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- **Serious Liver problems which may cause death, (liver toxicity)** have occurred in people who took maraviroc. An allergic reaction may happen before liver problems. **Symptoms of liver problems may include:** occur, and includes a rash on your body (allergic reaction), yellowing of the skin or whites of your eyes, dark urine, **nausea**, vomiting, stomach pain, **pale colored stools with bowel movements, loss of appetite, pain, aching on the right side below the ribs and liver damage** or elevated liver related function tests. People who have hepatitis B or C might be at higher risk of having liver problems.
- **Serious skin and allergic reactions which may cause death. In many cases people were taking other drugs that could also be responsible for these allergic reactions. These reactions include symptoms like rash, fever, wheezing, shortness of breath, swelling of the face or throat, tiredness, muscle or joint aches, ulcers in your mouth or blisters on your skin, mouth sores, or skin peeling or sloughing, redness or swelling of the eyes.**
- Heart problems, including heart attack.
- Low blood pressure when standing up, which can cause dizziness or fainting. People who have serious kidney problems may be at increased risk.

In addition to the serious side effects listed above, additional side effects include:

- Colds
- Cough
- Fever
- Rash
- Dizziness
- Diarrhea
- **Loss of appetite**
- **Blisters or sores in mouth**
- **Blisters or peeling of the skin**
- Swelling of parts of the body (**including redness or swelling of the eyes, mouth face or lips**)
- **Problems breathing**
- **Yellowing of the skin or the whites of eyes**
- Flu and flu-like symptoms
- Muscle aches, spasms and pain
- **Nausea/vomiting**
- **Right side pain, below ribs**
- Stomach pain and bloating
- Sleeping problems
- Runny, congested nose

- Problems with urination (**including dark or tea colored urine**)
- Low amounts of white blood cell counts (neutropenia)

Major Revision 7a NOTE: The following change applies to Appendix VI and VII – Sample Informed Consent Forms for the Tissue Subset - Rectal Component and Vaginal Component consents under – Your Participation is Voluntary

Participation in the Tissue Subset of this study is completely voluntary. You may decide not to participate. **[Tissue Subset sites to add this language: We may have slots available in both the main study and the Tissue Subset study. We will let you know which slots are still available.] Whatever you choose, Your decision not to participate in the Tissue Subset, and it will not have any impact on your participation in the main study, and will not result in any penalty or loss of benefits to which you are otherwise entitled. Whatever Even if you decide now, that you wish to participate in this part of the study, you may change your mind at any time. If this happens, you must tell the study staff that you have changed your mind.**

Major Revision 7b Appendix VI - Sample Informed Consent Form (Rectal Component) - Enrollment

You will have an enema to prepare the rectum for the rectal biopsy. A rectal biopsy is a procedure to remove a small piece of rectal tissue for examination. A rectal exam **will be is done first,** followed by collecting a fluid sample from your anal area using a small sponge. ~~The sponge draws the sample of the rectal fluid through a short hollow lubricated tube called an anoscope, which is placed into the rectum. After the anoscope is removed, then a~~ A lubricated instrument called a flexible sigmoidoscope **will be is** placed into the rectum. The biopsy can be taken...

Major Revision 7c Appendix VI - Sample Informed Consent Form (Rectal Component) - Week 24, 48, and 49 visits

At each of these visits, in addition to the procedures for which you have already consented, your blood will be drawn, up to 150 mL (which is about 30 teaspoons). A hair sample (about 100 hairs) will be collected. ~~and rectal tissues and fluids will be collected as described above.~~ **Fluid will be collected using a small sponge. The sponge draws the sample of the rectal fluid through a short hollow lubricated tube called an anoscope, which is placed into the rectum. Rectal tissue will be collected as described above.** All of these samples will be stored. You should not have...

Major Revision 7d Appendix VII - Sample Informed Consent Form (Vaginal Component) - Enrollment

Collection of Cervical Biopsies and Vaginal Fluids

A clinician will ask you about your menstrual cycle. These specimen collections will not occur during your menstrual period. We will offer you a planner (for example, a diary or a calendar) to help track your menstrual cycle. This will help us to schedule your biopsy appointments. A clinician will insert a speculum into your vagina to allow the clinician to see your vagina and

cervix. ~~Then the clinician will place a small sponge next to your cervix. The sponge will stay in place for a few minutes and will collect vaginal fluid. Then this will be removed.~~ Next, the clinician will collect up to three biopsies of the cervix using forceps. This instrument will pinch and cut out a small piece of the skin from the cervix (about the size of a grain of rice).

Major Revision 7e Appendix VII - Sample Informed Consent Form (Vaginal Component) - Week 24, 48, and 49 visits

At each of these visits, in addition to the procedures for which you have already consented, your blood will be drawn, up to 150 mL (which is about 30 teaspoons). A hair sample (about 100 hairs) will be collected. ~~The vaginal fluid and cervical biopsies will be collected as described above.~~ **by placing a sponge next to your cervix. The sponge will stay in place for a few minutes and will collect vaginal fluid. Then this will be removed.** Please note that up to three cervical biopsies will be collected at each of these visits **as described above**. All of these samples will be stored. You should not have...

IMPLEMENTATION OF MINOR REVISIONS

Minor Revision 1 Section 3.1 – Inclusion Criteria, seventh bullet, second sub-bullet

- Hemoglobin (men) > 11 g/dL, ~~absolute~~; Hemoglobin (women) ≥ 10.5 g/dL

Minor Revision 2 Section 3.1 – Inclusion Criteria, seventh bullet, sixth sub-bullet

- Alanine aminotransferase (ALST) and aspartate aminotransferase (ASLT) < 3 times the upper limit of normal (ULN)

Minor Revision 3 Section 3.6 – Participant Withdrawal, third paragraph

Every reasonable effort will be made to complete a final evaluation (as described in Sections 5.94 and 5.185 and Appendix I) of participants who terminate from the study prior to Week 49, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

Minor Revision 4a Section 5.8 – At Enrollment, second bullet

- Rectal and cervical tissue collection for GALT T cell phenotype (rectal tissue **only**) and *ex vivo* HIV challenge (rectal and cervicovaginal fluids are not collected at Enrollment)

Rectal and cervical tissue for GALT T cell phenotyping²⁰

¹⁰The chemistry panel includes: sodium, potassium, chloride, CO₂, glucose, creatinine, blood urea nitrogen, phosphate, creatinine clearance calculated using the Cockcroft-Gault formula, where CrCl (male) in mL/min = [(140 – age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL) and CrCl (female) in mL/min = [(140 – age in years) x (actual body weight in kg) x .85] / (72 x serum creatinine in mg/dL). **When calculating creatinine clearance, use the age and weight of the participant at the time the blood specimen is drawn. If the participant was not weighed at the visit when blood was drawn for serum creatinine testing, weight from the most recent previous visit may be used for the calculation. Record on the comment line the alternate collection date of the weight used. If weight and/or serum creatinine are reported by the lab to a higher level of precision than is allowed on the CRF, calculate the creatinine clearance before rounding. If any abnormalities...**

CONDITION AND SEVERITY ¹	STUDY DRUG USE	FOLLOW-UP AND MANAGEMENT ²
Hypophosphatemia		
Grade 2	Continue study drug	The phosphate should be repeated ideally within 4 weeks of the receipt of any initially abnormal results. If hypophosphatemia is confirmed, then a fractional excretion of phosphate should be calculated. Fractional excretion of phosphate is measured as: $FEPO_4 = \frac{\text{urine } [PO_4] \times \text{plasma } [Cr]}{\text{urine } [Cr] \times \text{plasma } [PO_4]} \times 100$ When the FEPO4 result is received, contact the PSRT for management instructions. <ul style="list-style-type: none"> • Supplemental phosphate...

_____ I agree to allow my blood to be tested to see how my genes make the drugs work in my
body.

_____ I **do** not agree to allow my blood to be tested to see how my genes make the drugs work in
my body.