

LETTER OF AMENDMENT #1 TO:

MTN-038

A Phase 1, Randomized, Pharmacokinetics and Safety Study of a 90 Day Intravaginal Ring Containing Tenofovir

Version 1.0, dated 11 July 2018

DAIDS Protocol #38460

IND #140,866

Date of Letter of Amendment: 4 December 2018

Site Instruction

The following information impacts the MTN-038 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 impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing participants of the contents of this Letter of Amendment (LoA).

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 a 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. A 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.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-038. The purpose of this LoA is to clarify the first study hypothesis to state that TFV and TFV-DP levels in PK samples will only be measurable in participants assigned to the TFV ring group. Other changes included in this LoA: removing the symbol and footnote about participants who have undergone supracervical hysterectomy or bilateral oophorectomy not subject to pregnancy testing and contraception counselling, updating the list of prohibited practices and products to include rectal products, adding guidelines for taking PrEP and PEP for participants who experience a known or potential HIV exposure during the study, adding specific criteria for stopping the MTN-038 study, correcting the number of visits at which cervical biopsy will be collected, and addition of the IND number assigned to the study.

Unless otherwise noted, text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions

The following revisions (1-2) were made to the first study hypothesis to clarify that TFV and TFV-DP levels will be measurable only in participants assigned to the TFV ring group.

1. Section 2.5.2, *Study Hypotheses*:

Plasma, CVF, and rectal fluid TFV levels and cervical tissue TFV and TFV-DP levels will be measurable in all **active arm** participants.

2. Section 10.3, *Primary Study Hypotheses*:

Plasma, CVF, and rectal fluid TFV levels and cervical tissue TFV and TFV-DP levels will be measurable in all **active arm** participants.

The following revisions (3-6) were made to remove language about participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records not subject to pregnancy testing and contraception counselling. These participants are not eligible for study participation; therefore the language is unnecessary.

3. Section 7, Visit Tables 4, 5, 8, 10, 11 and Appendix I:

Urine	• Pregnancy test ¶
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~~¶ Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records~~

LABORATORY										
URINE	Pregnancy test	X ¶	X ¶	*	*	X ¶	*	X ¶	X ¶	*

~~¶ Not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records~~

4. Section 7.7, after the second sentence:

~~Persons who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records are not required to receive contraceptive counseling.~~

5. Section 9.8, after the first sentence:

~~Pregnancy testing is not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records.~~

6. In Sample Informed Consent, under Important things you should know, fifth bullet point:

~~If your medical records confirm that you have had your uterus removed above the cervix or have had both ovaries removed, you will not have to have pregnancy testing performed.~~

The following revisions (7-9) were made to provide guidelines for taking PEP and PrEP for the clinical management of participants who experience a known or potential HIV exposure during the study.

7. Section 6.6, *Prohibited Medications*:

The use of **study product concurrently with PEP and PrEP** ~~are~~ **is** prohibited during study participation. **Individuals who need PEP or PrEP due to known or potential HIV exposure will permanently discontinue study product use. See Section 9.3 for additional information.** Use of anticoagulants or blood-thinners (such as heparin, Lovenox®, warfarin, and Plavix® [clopidogrel bisulfate]) is prohibited during study participation. ~~See Section 9.3 for additional information.~~

8. Section 9.3, *General Criteria for Temporary Hold and Permanent Discontinuation of Study Product*:

A participant will be permanently discontinued from IVR product use by the IoR/designee for any of the

following reasons:

- **Reported use of or need for PrEP or PEP.** Participants who experience a known or potential HIV exposure during study participation or have a recognized risk of exposure and thus need PEP or PrEP will have study product permanently discontinued and will be referred for PEP or PrEP initiation. Those who need PEP will be encouraged to start it as quickly as possible and within 72 hours of potential exposure. Since continued study follow-up would be of no benefit following permanent discontinuation of study product use, these participants will be exited from the study.

A participant will be temporarily discontinued from IVR product use (a product hold will be implemented) by the IoR/designee and a PSRT query submitted for any of the following reasons:

- ~~Reported use of PEP for HIV exposure~~
- ~~Reported use of PrEP for HIV prevention~~

9. Sample Informed Consent, *Why You May Be Withdrawn From The Study Without Your Consent:*

You may be removed from the study early without your permission if:

- **You report the use of or need for PEP or PrEP.**

The following revisions (10-11) were made to add rectal products to the list of prohibited products and practices in the protocol inclusion criteria and the prohibited practices and products table in the Sample Informed Consent.

10. Section 5.2, *Inclusion Criteria*, #13:

13) Per participant report at Screening and Enrollment, states a willingness to refrain from inserting any non-study vaginal **and rectal** products or objects into the vagina or rectum including, but not limited to spermicides, female condoms, diaphragms, intravaginal rings, vaginal or rectal medications, menstrual cups, cervical caps, douches, lubricants, and sex toys (vibrators, dildos, etc.) for the 24 hours preceding the Enrollment Visit and for the duration of study participation.

11. Sample Informed Consent, in the prohibited practices and products table:

<i>Activity:</i>	<i>For How Long?</i>
<ul style="list-style-type: none">• Use of vaginal and rectal products, including:<ul style="list-style-type: none">○ Spermicides○ Lubricants○ Contraceptive VRs○ Douches○ Vaginal medications○ Vaginal moisturizers	<ul style="list-style-type: none">• For the duration of study participation, beginning 24 hours before the enrollment visit

Other revisions:

12. In Section 9.4, *Temporary Product Hold/Permanent Discontinuation in Response to Adverse Events*, after the section on Grade 4 AE, specific criteria were added to specify the situations in which MTN-038 study will be halted or stopped.

Recruitment and Provision of Study Drug in MTN-038 will be halted if:

- **Review of AEs shows an unexpected, significant, or unacceptable risk to the participants enrolled in the study or treatment arm. AEs will be monitored by the Protocol Safety Review Team and a decision to discontinue the study because of safety will take into account whether the AEs were product-related, were serious, and/or led to participant discontinuation.**

- **Six or more subjects experience similar related Grade 3 or 4 AEs**

13. In Sample Informed Consent, under Important things you should know, fifth bullet point, the number of visits at which cervical samples will be collected was changed from 4 to 2:

- Vaginal and rectal fluids will be collected for research purposes and to test for STIs (if applicable). At 2 ~~4~~ visits, cervical tissue will also be collected;

14. Page 1 has been revised to add the IND number to the protocol title page

IND#: ~~[TBD]~~ **140866**

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

MTN-038

**A Phase 1, Randomized, Pharmacokinetics and Safety Study of a 90 Day Intravaginal Ring
Containing Tenofovir**

INVESTIGATOR SIGNATURE FORM

Version 1.0; July 11, 2018

Letter of Amendment #1, December 4, 2018

A Study of the Microbicide Trials Network

Funded by:

Division of AIDS (DAIDS), US National Institute of Allergy and Infectious
Diseases
US *Eunice Kennedy Shriver* National Institute of Child Health and Human
Development
US National Institute of Mental Health
US National Institutes of Health (NIH)

IND Holder:

Division of AIDS (DAIDS Protocol ID: 38460)

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference for Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., NIH, DAIDS) and institutional policies.

I agree to maintain all study documentation for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. DAIDS will inform the investigator/institution as to when these documents no longer need to be retained.

I have read and understand the information in the Investigator's Brochure(s), including the potential risks and side effects of the products under investigation, and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Investigator of Record (print)

Signature of Investigator of Record

Date