

LETTER OF AMENDMENT #03 TO:

MTN-039

**A Phase 1 Open Label Safety and Pharmacokinetic Study of Rectal Administration of a
Tenofovir Alafenamide/Elvitegravir Insert at Two Dose Levels**

Version 1.0, dated March 6, 2019

**DAIDS Protocol #38470
IND #145334**

Date of Letter of Amendment: 24 July 2020

Site Instruction

The following information impacts the MTN-039 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-039. The primary purpose of this LoA is to add an interim visit for additional safety evaluation before resuming study visits for participants who experience a gap of more than 60 days between visits due to a pause in the study. This LoA also clarifies that some visit procedures may be conducted remotely to mitigate potential hazards to participants or due to public health emergencies at the study sites; clarifies that the study should ideally aim to enroll and assign three participants assigned female sex at birth to each sample collection group; adds Tenofovir (TFV) to the primary pharmacokinetics endpoints; changes pregnancy testing from "if indicated" to being required at the two dosing visits for participants with childbearing potential; clarifies that the overall study duration may be affected by COVID-19 closures; corrects an inconsistency regarding prohibited medications between the protocol and the Informed Consent Form; and updates the Protocol Team Roster.

Unless otherwise noted below, text to be deleted is noted by ~~strike through~~, text to be added is noted in **bold**, and text in **bold italics** is not to be added, but to serve as a clarification of the implementation item in question.

Detailed Listing of Revisions

The following revisions (1-2) were made to add an interim visit for additional safety evaluation before resuming study visits for participants who experience a gap of over 60 days between visits due to a pause in the study.

1. After the third sentence of the first paragraph of Section 7.6, *Interim Visits*:

Interim visits may be performed at any time during the study, and any visit procedures may be conducted as indicated. All interim contacts and visits will be documented in participants' study records. If a participant misses a visit (e.g., presents to the clinic outside of the visit window), the participant can return for an interim visit to make up certain missed visit procedures and specimen collections. **If a gap of over 60 days occurs between visits for a participant, the participant will be asked to return for an interim visit for additional safety evaluation prior to the next scheduled visit to confirm the absence of any clinical symptoms, recent illness, or acquisition of HIV or STIs.** Refer to the MTN-039 SSP Manual for additional details.

2. After the fourth bullet point of the first paragraph in "Other Procedures" sub-section of Appendix III, *Sample Informed Consent Form (Screening, Enrollment, Long-term Storage and Future Testing)*:

In addition to the procedures listed above, it is possible that study clinicians may need to perform additional tests, if necessary (e.g., if you report having symptoms of a urinary, genital, or other infection and/or other issues, **or if you experience a gap of over 60 days between visits due to a pause in the study**). These tests might include the following:

- Physical exam
- Pelvic exam
- Genital exam
- Rectal exam
- Test rectal or throat samples for STIs
- Test cervix/vaginal samples for STIs
- Test your urine for STIs or other infections
- Test your blood for STIs **and HIV**
- Test your blood to check the health of your blood, liver and kidneys
- Give you treatment or refer you for treatment of STIs or other issues, if needed.

3. The following clarifications were made to the "Study Duration" sub-section of the Protocol Summary, to the first sentence of Section 4.4., *Time to Complete Accrual*, and to the first sentence of Section 10.6, *Participant Accrual, Follow-up and Retention*; and was added at the end of each section:

Approximately 6-13 weeks of follow-up per participant is planned with a projected accrual period of 6-8 months. The total duration of the study will be approximately 11 months.*

The time to complete accrual is anticipated to be approximately 6-8 months.*

Based on previous studies of rectal products with similar eligibility requirements, the accrual of approximately 20 eligible participants will take approximately 6-8 months.*

*** Overall study duration - from first enrollment through closure of all follow-up - may be longer than planned if temporary site closures due to the COVID-19 pandemic cause a delay or pause in enrolling participants at one or more research sites.**

The following revisions (4-5) were made to allow certain visit procedures to be conducted remotely in order to reduce risks for participants.

4. After the first paragraph in Section 7, *Study Procedures*:

For all study visits, sites may utilize telephone or online applications to conduct appropriate visit procedures in a remote fashion in order to limit time spent in the clinic. This may include, but is not limited to, remotely conducting interviews, providing protocol counseling and administering CASI surveys, when applicable. Any modifications to study visits will be documented accordingly in the study database.

5. After the second sentence in “Who will be in this research study and what will I be asked to do if I join?” sub-section of Appendix III, *Sample Informed Consent Form (Screening, Enrollment, Long-term Storage and Future Testing)*:

The study includes a total of 10 clinic visits and one final contact, including the Screening Visit which is taking place today. All clinical visits will take place at this study clinic. **For all study visits, you may be asked to conduct certain visit procedures via phone or online application when applicable to reduce your time spent in the clinic.**

The following revisions (6-7) were made to clarify that the study should ideally aim to enroll and assign three participants assigned female sex at birth to each of the two sample collection groups, but it is not a requirement.

6. The last sentence of the second paragraph in Section 7.3, *Enrollment (Day 0)*:

Ideally At least three participants assigned female sex at birth should be enrolled and assigned to each group.

7. The last sentence of the second paragraph in Section 10.5, *Randomization Procedures*:

Randomization will be stratified by sex at birth to **ideally** incorporate at least three participants assigned female sex at birth in each group.

The following revisions (8-9) were made to make the pregnancy test from “if indicated” to being required at the two dosing visits (Visits 3 and 7) for participants of childbearing potential.

8. In Table 12 of Section 7.4.1, *Dosing – Visits 3 and 7*, and Appendix I, *Schedule of Study Visits and Evaluations*

Urine	<ul style="list-style-type: none"> • NAAT for GC/CT*▼ • Urine dipstick/culture* • Pregnancy test*■
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		Screening Visit 1	Enrollment Visit 2 (Day 0)	Dosing Visits 3, 7	24 hours Post- Dosing Visits 4 and 8	Other Post- Dosing Visits 5, 6, 9, and 10	Final Contact/Early Termination Visit 11
URINE	NAAT for GC/CT▼	X	*	*	*	*	*
	Pregnancy test ■	X	X	* X	*	*	*

9. Before the first item of the seventh bullet point in the “Dosing Visits (Visits 3 and 7)” sub-section of Appendix III, *Sample Informed Consent Form (Screening, Enrollment, Long-term Storage and Future Testing)*:

- If applicable:
 - **Have a urine test for pregnancy and discuss with study staff ways to avoid getting pregnant**
 - Have vaginal fluid collected with a swab

The following revisions (10-13) were made to add measurement of TFV to the primary pharmacokinetics endpoints throughout the protocol.

10. After the fourth bullet point of the “Primary Endpoints” sub-section in *Protocol Summary*:

- **TFV concentration in:**
 - **Rectal mucosal tissue homogenates**

11. After the fourth bullet point of the “Primary Endpoints” sub-section in Section 4.2, *Summary of Major Endpoints*:

- **TFV concentration in:**
 - **Rectal mucosal tissue homogenates**

12. Under the bullet point “pharmacokinetics” of Section 10.2, *Study Endpoints*:

- **TFV concentration in:**
 - **Rectal mucosal tissue homogenates**

13. In the second row, under the third bullet point “11 samples for PK” of the rectal tissue column in Table 16, *Specimens to be Collected to Assess Safety, PK and Ex Vivo Antiviral Activity*:

Study Visit	Specimens collected for PK, PD and mucosal safety			
	Blood	Rectal Fluid	Rectal Tissue	CVF
Visit 3 & Visit 7 - Samples collected at 1, 2, 4 and 6 hours	<ul style="list-style-type: none"> • Blood for PK 	Group 1 at 2-hour <ul style="list-style-type: none"> • RF for microbiome • RF for PK • RF for PD Group 1 at 6-hour <ul style="list-style-type: none"> • RF for PK Group 2 at 4-hour <ul style="list-style-type: none"> • RF for PK 	Group 1 only at 2-hour <ul style="list-style-type: none"> • 7 samples for biomarkers • 4 samples for PD • 11 samples for PK <ul style="list-style-type: none"> ○ 1 for EVG ○ 1 for TFV† and TFV-DP ○ 1 for backup ○ 8 for MMC isolation 	Group 1 at 2-hour <ul style="list-style-type: none"> • CVF for microflora • CVF for PK • CVF for PD Group 1 at 6-hour <ul style="list-style-type: none"> • CVF for PK Group 2 at 4-hour <ul style="list-style-type: none"> • CVF for PK

14. The following clarification applies to Section 13, *Human Subjects Protections*. An asterisk is added to the end of the first sentence of the first paragraph with the clarification description added at the end of the paragraph:

Site investigators will make efforts to minimize risks to participants.*

**** Deviations from this protocol may be implemented by investigators prior to IRB/IEC approval, if those deviations are required to eliminate apparent immediate hazards to the study participant. [See 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements.] Any effort made to minimize risks to participants outside of procedures listed in the protocol document must be documented as Protocol Deviations and reported to the Protocol Team and IRB/IEC as soon as possible. [See ICH E6(R2), Good Clinical Practice, Section 4.5.4.] In the event of a public***

health emergency, investigators should adhere to the recommendations of their local institutions, IRB/IEC and local health departments. When conflicts exist between local directives, MTN, Protocol Team and/or DAIDS policies or guidance, sites should follow the requirement that is most protective of study participants and site staff. [See DAIDS Guidance, Coronavirus Disease (COVID-19) and DAIDS HIV/AIDS Network Clinical Research Studies, Page 3, dated March 13, 2020.]

15. The following revision was made to the sixth bullet point of the first paragraph in “Is it possible that I may be taken out of the study without my consent?” sub-section of Appendix III, *Sample Informed Consent Form (Screening, Enrollment, Long-term Storage and Future Testing)*:

- You report the use of the following prohibited medications:
 - a. Anticoagulants (e.g., heparin, Lovenox, warfarin and Plavix)
 - b. Certain CYP3A strong/moderate inhibitors or inducers (~~e.g., grapefruit, Prozac, Zoloft, Prednisone, Prilosec~~)

16. Protocol Team Roster – Removal: Jennifer Thomas, Mark Marzinke

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17. Protocol Signature Page was updated to include Letter of Amendment #03; it is appended to the end of this document.

The above information, as well as the changes from LoA#01 and LoA#02, will be incorporated into the next version of the protocol at a later time if it is amended.

MTN-039

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INVESTIGATOR SIGNATURE FORM

Version 1.0; March 6, 2019

Letter of Amendment #01; 20 September 2019

Letter of Amendment #02; 23 March 2020

Letter of Amendment #03; 24 July 2020

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:

DAIDS (DAIDS Protocol ID: 38470)

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