

LETTER OF AMENDMENT #01 TO:

MTN-035

Acceptability, Tolerability, and Adherence of Three Rectal Microbicide Placebo Formulations among HIV Seronegative Cisgender Men, Transgender Men and Transgender Women Who Engage in Receptive Anal Intercourse

Version 1.0, dated 15 June 2018

DAIDS Protocol #38459 A Non-IND Study

Date of Letter of Amendment: 6 January 2020

Site Instruction

The following information impacts the MTN-035 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. 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. DAIDS sites are still required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). DAIDS 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-035. The primary purpose of this LoA is to allow study sites to forego the short message service (SMS)/instant messaging (IM) procedures for collection of adherence and acceptability data when the SMS/IM system malfunctions, or to forego them entirely at any site(s) lacking the necessary infrastructure to reliably use SMS/IM for data collection. In those instances, data that would otherwise be collected via SMS/IM will be collected during the in-depth interviews (IDI) taking place at the product use end visits (PUEV). This LoA also modifies the provision of lubricant to be a required visit procedure at all study visits, and updates several DAIDS document web links.

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 (#1-5) allow site staff to collect adherence and acceptability data that would otherwise be collected via SMS/IM between study visits to instead be collected via IDI at the PUEVs, either when the SMS/IM system malfunctions at a site with SMS/IM capacity or at sites that lack the capacity to carry out the SMS/IM procedures.

1. "Behavioral/Counseling" sections of Table 5: Visit 2 – Enrollment Visit in Section 7.3, *Enrollment (Day 0)*, and Appendix I, *Schedule of Study Visits and Evaluations*:

Training in short message service (SMS)/instant message (IM) Reporting System **(at sites with capacity)**

2. Second paragraph of Section 7.4.1, *Visits 3, 5 and 7 – First, Second and Third Product Use End Visits (PUEV)*:

Barring any technical or connectivity issues, Pparticipants at sites with capacity will complete brief, weekly short SMS/IM assessments about their product use and RAI behaviors during each 4-week product use period. Behavioral evaluations will be completed at the end of each product use period at Visits 3, 5, and 7, including a brief in-depth interview (IDI) during the visit to review their SMS/IM reports, **or their product use and RAI behaviors during the previous 4-week product use period if unable to complete the SMS/IM assessments.**

3. Second paragraph and first sentence of third paragraph in Section 7.8, *Behavioral Evaluations*:

Barring any technical or connectivity issues, Pparticipants at sites with capacity will also complete a brief weekly report of product use via SMS/IM for each study product. A brief IDI is planned for all participants at the three PUEVs (Visits 3, 5 and 7). These IDIs will review and explore participants' responses to acceptability, tolerability, and adherence questions asked via SMS/IM during each product use period; **if participants were unable to complete the SMS/IM assessments, these IDIs will explore their product use and RAI behaviors during each period.**

Based on Behavioral Research Working Group (BRWG) review of SMS/IM data **(or data from the brief IDIs at sites without SMS/IM capacity)**, approximately 10 participants per site will be selected and invited to complete a longer IDI at the Final Visit (Visit 8).

4. Seventh bullet point in "Enrollment Visit" section of Appendix III, *Sample Informed Consent Form (Screening and Enrollment)*:

- **[SITES TO MODIFY IF DO NOT HAVE SMS/IM CAPACITY]:** Be asked to respond to weekly electronic messages related to your use of the study products during each product use period.

5. Sixth bullet point in "Product Use End Visits (PUEV) – Visits 3, 5, and 7" section of Appendix III, *Sample Informed Consent Form (Screening and Enrollment)*:

- **[SITES TO MODIFY IF DO NOT HAVE SMS/IM CAPACITY]:** Be asked to take part in a brief interview (~15 minutes) about your responses to the electronic messages during the previous month of product use.

The following revisions (#6-11) modify the sites' offering of lubricant to participants to be a required visit procedure at all study visits.

6. Section 6.6, *Ancillary Study Supplies*:

Participants will be offered male condoms **and personal lubricant (not containing N-9)** at all visits. The condoms **and lubricant** will be made available in the clinic and will be dispensed by the clinic staff. Participants will be provided lubricant approved for use during the product administration periods to facilitate insertion. ~~At all other visits, clinical staff will offer participants lubricant (not containing N-9) as per local standard of care.~~

7. "Study Product/Supplies" sections of Table 4: Visit 1 – Screening Visit in Section 7.2, *Screening Visit*, Table 5: Visit 2 – Enrollment Visit in Section 7.3, *Enrollment (Day 0)*, Table 6: Visits 3, 5 and 7 – First, Second and Third PUEV in Section 7.4.1, *Visits 3, 5 and 7 – First, Second and Third Product Use*

End Visits (PUEV), Table 7: Visits 4 and 6 – Product Switch Visits in Section 7.4.2, *Visits 4 and 6 – Product Switch Visits*, and Table 8: Visit 8 – Final/Early Termination Visit in Section 7.4.3, *Visit 8 – Final/Early Termination Visit*.

- Offer lubricant ~~**~~

~~** Lubricant will be provided at product administration visits and as per local standard of care at other visits~~

8. “Study Products/Supplies” section of Appendix I, *Schedule of Study Visits and Evaluations*:

	Visit 1 SCR	Visit 2 ENR	Visits 3, 5 & 7 PUEV 1-3	Visits 4 & 6 Product Switch Visits	Visit 8 Final/Early Term Visit
Offer lubricant	**X	**X	**X	**X	**X

~~** Lubricant will be provided at product administration visits and as per local standard of care at other visits~~

9. Fourth-to-last bullet point in “Screening Visit” section, fourth-to-last bullet point in “Product Use End Visits (PUEV) – Visits 3, 5, and 7” section, and second-to-last bullet point in “Final/Early Termination Visit – Visit 8” section of Appendix III, *Sample Informed Consent Form (Screening and Enrollment)*:

- Be given male condoms **and lubricant**, if you need them.
- ~~[SITES TO SPECIFY IF PARTICIPANTS MAY BE OFFERED LUBRICANT PER LOCAL STANDARD OF CARE].~~

10. Fourth-to-last bullet point in “Enrollment Visit” section and fourth-to-last bullet point in “Product Switch Visits – Visits 4 and 6” section of Appendix III, *Sample Informed Consent Form (Screening and Enrollment)*:

- Be given male condoms **and lubricant**, if you need them.

11. Second-to-last bullet point in “What are the possible benefits from taking part in this study?” section of Appendix III, *Sample Informed Consent Form (Screening and Enrollment)*:

- You will receive free male condoms **and lubricant**, if you need them.
- ~~You may receive free lubricant per local standard of care.~~

Additional minor modifications include:

12. Section 7.10, Specimen Management, first sentence:

The study site will adhere to the standards of good clinical laboratory practice (<https://www.niaid.nih.gov/sites/default/files/gclp.pdf>), in accordance with **DAIDS Laboratory Policy** (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>) ~~current DAIDS Laboratory Requirements~~, MTN-035 SSP Manual (<http://www.mtnstopshiv.org/studies>), and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures.

13. Section 7.11, DAIDS Laboratory Oversight, first sentence:

All laboratories participating in DAIDS Sponsored and/or Funded Laboratories in Clinical Trials will adhere to the DAIDS Laboratory Policy. (~~<https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs>~~) (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>)

14. Section 8.3.1, *Adverse Events*, last sentence of third paragraph:

AE severity will be graded per the DAIDS Table for Grading Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017 and/or Addenda 1, 2 and 3 (Female Genital [Dated November 2007], Male Genital [Dated November 2007] and Rectal [Clarification Dated May 2012] Grading Tables for Use in Microbicide Studies), available on the DAIDS Regulatory Support Center (RSC) website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables> <https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables>.

15. Section 8.3.2, *Serious Adverse Events*, first sentence:

An SAE will be defined by the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, January 2010), which is available on the DAIDS RSC website at <http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual> — <https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids>, as an AE that:

16. Section 11.3, *Quality Control and Quality Assurance*, first sentence:

The study site will conduct quality control and quality assurance procedures in accordance with current DAIDS policies. (https://www.niaid.nih.gov/sites/default/files/qmppolicy_0.pdf)

17. Protocol references to the Truvada Package Insert were updated to the most current version dated May 2018.

18. The Protocol Signature Page was updated to include Letter of Amendment #01 and is appended to the end of this document.

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

APPENDIX: MTN-035 INVESTIGATOR SIGNATURE FORM

MTN-035

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INVESTIGATOR SIGNATURE FORM

Version 1.0; June 15, 2018
Letter of Amendment #01; January 6, 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 Sponsor:

A Non-IND Study (DAIDS Protocol ID: 38459)

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