LETTER OF AMENDMENT #02 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 2.0, dated 16 December 2014

DAIDS Protocol #11985
IND #108,743

Date of Letter of Amendment: 28 March 2018

Site Instruction

The following information impacts the MTN-025 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. 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-025. The primary purpose of this LoA is to include language allowing international regulatory authority review of study records in both the protocol and informed consent. This LoA also clarifies data management and documentation storage language for the in-depth interview (IDI) and focus group discussion (FGD) source data/documents, updates the Investigator Signature Page, corrects an inconsistency by copying the Exploratory Endpoints previously listed only in the Protocol Summary into Section 4 of the protocol, incorporates the protocol document changes made with Clarification Memos (CM) #1 and #2, updates the Protocol Team Roster, and makes other minor revisions to the protocol.

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 (#1-6) allow international regulatory authority review of study records:

1. Section 12, Clinical Site Monitoring, last paragraph, second sentence:

   The IoR/designee will also allow inspection of all study-related documentation by authorized representatives of the MTN LOC, SDMC, and LC; NIAID, FDA, IPM, OHRP**, IRBs/ECs,** and **other** local**,** ~~and~~ US**, or international** regulatory authorities.

2. Section 13.1, Institutional Review Boards/Ethics Committees, first paragraph, last sentence:

   ~~The~~ IoR**s/designees** will permit audits by the NIH, IPM, the FDA, OHRP, **MTN LOC, IRBs/ECs, SDMC, and other local, US, or international regulatory authorities,** or any of their appointed agents.

3. Section 13.6, Participant Confidentiality, first bullet point:

   Representatives of the US Federal Government, including the US FDA, the US OHRP, NIH, and/or contractors of the NIH, and other local**,** ~~and~~ US**, or international** regulatory authorities

4. Appendix IV, Sample Informed Consent Document (Screening), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

5. Appendix V, Sample Informed Consent Document (Enrollment), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

6. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Confidentiality, second bullet point:

   Other local, US, or international regulatory authorities [Insert applicable local authorities, e.g., Ministry of Health, medicine control authority]

The following revisions (#7-9) clarify/specify data management and documentation storage for the IDI and FGD source data, including audio recordings:

7. Section 11.1, Data Management Responsibilities, second paragraph, first sentence, has been revised to describe the source data management process and to explicitly list which documents will be considered as source data for the qualitative behavioral evaluations (i.e., IDIs and FGDs):

   Transcriptions of interviews ~~Interview~~ and group discussion**s** ~~files~~ (if applicable) **will be** generated **using the audio recordings. Both the audio recordings and the transcripts** ~~in the field~~ will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be uploaded and managed using a qualitative software package. **Interview and group discussion notes (if applicable) will be kept at the site in the participant files. The qualitative data from MTN-025 will include three main data sources: original handwritten notes of IDIs and FGDs, audio-recorded IDIs and FGDs, and transcripts of IDIs and FGDs.**

8. Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions, third paragraph, fifth sentence has been revised and last sentence has been added, to explicitly include audio recordings as one of the documents considered to be source data and to disclose to participants how long the audio recordings will be stored:

   Your audio recordings and any other ~~The~~ information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-025(HOPE) study team for the purposes of this research. ***[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs:*** **The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.]**

9. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Risks and/or Discomforts, second paragraph, last sentence, has been added to explicitly disclose to participants how long the audio recordings will be stored:

   [Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: **The audio recordings, notes, and transcripts from these materials will be kept for at least two years after the vaginal ring is approved for marketing or two years after all developmental research on the vaginal ring is stopped.]**

The following revision updates the Investigator Signature Form language describing the investigators' responsibilities as per DAIDS requirements (see Appendix at the end of this LoA for the updated Investigator Signature Form):

10. Investigator Signature Form, first paragraph:

    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 will comply with all requirements regarding the obligations of investigators as outlined in the Statement of Investigator (Form FDA 1572), which I have also signed.~~

[new paragraph] 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.** ~~following the date of marketing approval for the study product for the indication in which it was studied. If no marketing application is filed, or if the application is not approved, the records will be retained for two years after the investigation is discontinued and the US Food and Drug Administration is notified. Publication of the results of this study will be governed by MTN policies. Any presentation, abstract, or manuscript will be submitted to the MTN Manuscript Review Committee, DAIDS, IPM and other entities for review prior to submission, as required by the MTN Publication Policy.~~

The following revision corrects an inconsistency by copying the Exploratory Endpoints previously listed only in the Protocol Summary into Section 4, Study Design, as per our usual practice:

11. Section 4.2, Summary of Major Endpoints, after Secondary Endpoints:

Exploratory Endpoints:

1. **Understanding of efficacy**
   - **Self-reported understanding of partial efficacy**

2. **Understanding of ring acceptability in the context of known efficacy**
   - **Self-reported product acceptability and attitudes towards combination prevention**

3. **Feasibility:**
   - **Participant report of product storage issues and feasibility regarding the follow-up schedule**
   - **Visit retention**
   - **Proportion of returned rings (used and unused)**

4. **Genital microenvironment**
   - **In genital swab samples, candidate biomarkers of safety, adherence and efficacy, HIV exposure and antiretroviral resistance, and genital microflora**

5. **Characterization of MTN-020 participants who do not enroll in MTN-025**
   - **Participant report of the factors that led to her decision to decline enrollment into MTN-025**

6. **Characterization of MTN-020 participants who do not accept study product in MTN-025**
   - **Participant report of the factors that led to her decision to not accept study product**

7. **Exploration of alternative markers of adherence**
   - **Hair dapivirine levels**
   - **Self-reported product use**

The following revisions (#12-17) update the URLs where current DAIDS guidance documents can be found:

12. Section 7.13, Specimen Collection and Processing:

Each study site will adhere to the standards of good clinical laboratory practice (https://www.niaid.nih.gov/sites/default/files/~~documents/~~gclp.pdf)

13. Section 7.14, Specimen Handling:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. ~~(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)~~ **(https://www.niaid.nih.gov/research/daids-clinical-research-policies-us-labs~~)~~**

14. Section 8.4.1, Adverse Event Reporting to DAIDS:

    In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, http://rsc.tech-res.com/clinical-research-sites/safety-reporting/~~daids~~**daers**/paper-eae-reporting.

15. Section 11.2, Source Documents and Access to Source Data/Documents:

    All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/~~documents/~~daids-sourcedocpolicy.pdf) and the relevant appendix regarding source documentation (https://www.niaid.nih.gov/sites/default/files/~~documents/~~sourcedocappndx.pdf).

16. Section 11.3, Quality Control and Quality Assurance:

    All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites (https://www.niaid.nih.gov/sites/default/files/~~documents/~~qmppolicy.pdf).

17. Section 13.5, Informed Consent Process:

    Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials (https://www.niaid.nih.gov/sites/default/files/~~documents/~~daids-sourcedocpolicy.pdf).

The following revisions (#18-21) incorporate the changes to protocol text made with CM #1:

18. Section 7.3, Enrollment Visit (Day 0): Table 6, Enrollment Visit has been modified to correct the omission of an asterisk indicating that the insertion of one study vaginal ring at the Enrollment Visit is an "if indicated" procedure, see bolded text below:

Table 6: Enrollment Visit

Study Product/Supplies	• Offer condoms • Provision of study VR use instructions* • Offer and, if accepted, provide study VR(s) • Insertion of one study VR***** • Digital exam by clinician to check VR placement*

19. Section 7.11, Laboratory Evaluations, has been modified to add language at the end of the section regarding hair collection for consistency with similar language elsewhere in the protocol and consent forms:

    IPM or MTN Designated Laborator**ies**~~y~~:
    - Study Product- Vaginal Ring
      - Adherence assessment(s)
    - **Hair for biomarkers and archive**

20. Section 7.13, Specimen Collection and Processing, has been modified to update the URL where the current DAIDS standards of good clinical laboratory practice can be found:

    Each study site will adhere to the standards of good clinical laboratory practice ~~(http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf)~~
    (https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)

21. Section 7.14, Specimen Handling, has been modified to update the URL where the current DAIDS Laboratory Policy can be found:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials~~.~~
~~(http://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/documents/labpolicy.pdf)~~**(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)**

The following revisions (#22-26) incorporate the changes to protocol text made with CM #2:

22. The following modifications were made to delete language related to cervical fluid collection that remained in the protocol text due to an administrative error, as there are no cervical fluid samples being collected for research purposes in this study:

    a) Appendix V: Sample Informed Consent Document (Enrollment), *What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?*:

    - Provide vaginal fluid ~~and cervical fluid~~ samples:
      - To see how the dapivirine vaginal ring protects against HIV and to explore the health of the female genital tract. The vaginal fluid ~~and cervical fluid~~ collected will be used for research purposes only.

    b) Appendix V: Sample Informed Consent Document (Enrollment), *Consent for Storage and Future Testing of Specimens*:

    There might be a small amount of blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your leftover blood, hair, **and** vaginal fluid~~, and cervical fluid~~ samples, and related health information for use in future studies… You can still enroll in this study if you decide not to have leftover blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored for future studies. If you do not want the left-over blood, hair, **and** vaginal fluid ~~and cervical fluid~~ samples stored, we will destroy these left over specimens.

23. The following modifications were made to Section 6.4.2, Study Product Dispensing, to clarify that the IoR designee can also use their discretion to provide additional rings to participants unable to attend their next scheduled visit:

    If the participant is unable to attend her next scheduled visit an additional ring(s) may be provided at the discretion of the IoR**/designee** as permitted in the SSP…

    … If a participant requires an additional ring for any reason, at a time other than when she is scheduled to receive one, additional product may be dispensed at the discretion of the IoR**/designee**.

24. The following modifications were made to clarify that hair sampling procedures are optional at each study visit, to be consistent with hair sampling language in the sample informed consent:

    a) Tables in Section 7.4.1 – Months 1 and 2, Section 7.4.2 – Quarterly Visits (Months 3, 6, 9), Section 7.4.3 – Product Use End Visit (PUEV), and Section 7.4.4 – Study Exit/Termination Visit, only row under "Hair":

    - Collect hair **(required unless participant declines)**

    b) Appendix I, Schedule of Study Visits and Evaluations, only row under "Hair":

    Hair sample(s) for DPV testing and archive **(required unless participant declines)**

25. The following modifications were made to Section 11.1, Data Management Responsibilities, to explicitly state that the overall data management system used in this study adheres to the US-EU Safe Harbor requirements and the EU Data Protection Directive 95/46/EC and is both ICH GCP and CFR compliant, along with a note clarifying how paperless data collection is being rolled out in the HOPE study:

    Study CRF data are **entered into the MTN-025 database,** transferred **in compliance with the US-EU Safe Harbor Requirements and the EU Data Protection Directive 95/46/EC** to the MTN SDMC, ~~entered,~~ and cleaned using **Medidata Rave, a**~~the~~ data management system **compliant with the International Council on Harmonization (ICH) Good Clinical Practices (GCP) and US CFR guidelines for electronic data capture**.

26. The following modifications were made to update the URLs where current DAIDS guidance documents can be found:

a) Section 7.13, Specimen Collection and Processing:

Each study site will adhere to the standards of good clinical laboratory practice ~~(https://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/gclp.pdf)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/gclp.pdf)**

b) Section 7.14, Specimen Handling:

Specimens will be handled in accordance with current requirements for DAIDS Sponsored and/or Funded Laboratories in Clinical Trials. ~~(https://www.niaid.nih.gov/labsandresources/resources/daidsclinrsrch/Pages/Laboratories.aspx)~~ **(https://www.niaid.nih.gov/sites/default/files/documents/laboratorypolicy1.pdf)**

c) Section 8.4.1, Adverse Event Reporting to DAIDS:

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/manual**.

d) Section 8.4.1, Adverse Event Reporting to DAIDS:

In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE Form. This form is available on the RSC website, ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids/paper-eae-reporting**.

e) Section 8.4.3, Grading Severity of Events:

The most current DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014, and the Female Genital Grading Table for Use in Microbicide Studies (Addendum 1 to the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, November 2014 [Dated November 2007]), will be used and is available on the RSC website at ~~http://rsc.tech-res.com/safetyandpharmacovigilance/~~**http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables**.

f) Section 11.2, Source Documents and Access to Source Data/Documents:

All study sites will maintain source data/documents in accordance with Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocpolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)** and the relevant appendix regarding source documentation ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/sourcedocappndx.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/sourcedocappndx.pdf)**.

g) Section 11.3, Quality Control and Quality Assurance:

All study sites will conduct quality control and quality assurance procedures in accordance with Requirements for Clinical Quality Management Plans at DAIDS Funded and/or Supported Clinical Research Sites ~~(http://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdfhttp://www.niaid.nih.gov/LabsAndResources/resources/DAIDSClinRsrch/Documents/qmppolicy.pdf)~~**(https://www.niaid.nih.gov/sites/default/files/documents/qmppolicy.pdf)**.

h) Section 13.5, Informed Consent Process:

Study staff must document the informed consent process in accordance with the Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials ~~(http://rsc.tech-res.com/policiesandregulations/)~~**(https://www.niaid.nih.gov/sites/default/files/documents/daids-sourcedocpolicy.pdf)**.

Additional minor modifications include:

27. Protocol Team Roster- Updates, including those made with CM #1:

    a) From CM #1:
        - Gonasagrie Nair will be Site Investigator of Record for the Cape Town Emavundleni CRS instead of the CAPRISA eThekwini CRS.
        - Logashvari Naidoo will be Site Investigator of Record for the MRC-Chatsworth CRS instead of the MRC-Tongaat CRS.
        - Zip codes for all US NIH protocol team roster members changed from 20892 to 20852.
        - Addresses for all MTN LOC – FHI 360 protocol team roster members edited to add FHI 360 and remove P.O. Box 21059.
        - Ashley Mayo's title changed to Sr. Clinical Research Manager.
        - MRC CTU Site Investigator titles for Zakir Gaffoor, Nitesha Jeenarain and Samantha Siva changed to CRS Leader.

    b) Current updates:
        - Vimla Naicker will be Site Investigator of Record for the MRC-Tongaat CRS and the MRC-Verulam CRS instead of the MRC-Botha's Hill CRS.
        - Zakir Gaffoor will be CRS Leader for the MRC-Verulam CRS instead of the MRC-Chatsworth CRS.
        - Nitesha Jeenarain will be CRS Leader for the MRC-Chatsworth CRS instead of the MRC-Verulam CRS.
        - The name of the University of Zimbabwe-University of California San Francisco Collaborative Research Program (UZ-UCSF) Clinical Trials Unit was changed to University of Zimbabwe College of Health Sciences Clinical Research Centre (UZCHS-CTRC).
        - Email addresses for all UZCHS-CTRC protocol team roster members edited to change @uz-ucsf.co.zw to @uzchs-ctu.org.
        - Luis Duran's title changed to Project Manager.
        - Devika Singh's address was changed to 19 Randall Drive, Jericho, VT 05465 USA, her phone number was changed to 206-920-0975, and her fax number was removed.

28. Protocol Team Roster- Removals, including those made with CMs #1 and #2:

    a) From CM #1: Danielle Crida, Newton Kumwenda, Jeffrey Stringer, Vaneshree Govender, Beth Galaska, Kailazarid Gomez, and Fatima Glyn Zulu.

    b) From CM #2: Ken Ho, Ian McGowan.

    c) Current removals: Arendevi Pather, Anamika Premrajh, Nishanta Singh, Francis Martinson, Ellen Conser, Jennifer Berthiaume.

29. Protocol Team Roster- Additions, including those made with CM #1:

    a) From CM #1:

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b) Current additions:

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

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

INVESTIGATOR SIGNATURE FORM

Version 2.0; December 16, 2014
Letter of Amendment #01; April 11, 2016
Letter of Amendment #02; March 28, 2018

A Study of the Microbicide Trials Network

Funded by:
Division of AIDS, 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

IND Holder:
International Partnership for Microbicides (IPM) (DAIDS Protocol ID: 11985)

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

_____ _____
Signature of Investigator of Record Date