

**LETTER OF AMENDMENT #01 TO:**

**MTN-034**

**A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population**

**Version 2.0, dated 7 December 2017**

**DAIDS Protocol #12066  
IND #139,598**

**Date of Letter of Amendment: 4 September 2018**

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*Site Instruction*

The following information impacts the MTN-034 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-034. The primary purpose of this LoA is to add language in the protocol and consent forms describing the study sponsor's responsibilities related to provision of clinical trials insurance for sites that do not already provide this insurance, and to clarify data management and documentation storage language for the study's source data/documents. This LoA also clarifies that the dried blood spot assessments will only be done for participants taking Truvada, removes mention of referral of pregnant participants to MTN-016 for consistency across consent forms, removes a breast assessment from the list of required physical exam procedures, and updates the IND number, Protocol Team Roster and DAIDS Laboratory Policy web link.

Text to be deleted is noted by ~~strike through~~ and text to be added is noted below in **bold**.

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*Detailed Listing of Revisions*

*The following revisions (#1-3) add language in the protocol and consent forms describing DAIDS responsibilities related to provision of clinical trials insurance for sites that do not already provide this insurance*

1. Section 13.8, Compensation, after the first paragraph:

**If a participant becomes ill or injured as a result of participation in this trial, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer the participant for ongoing treatment for the injury, if needed. The study sponsor will be responsible for providing insurance to cover appropriate medical expenses for treatment of any such illness or injury, if the site does not already provide this insurance. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation.**

- Appendix V, Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-term Storage), "RESEARCH-RELATED INJURY" section:

~~[SITES TO SPECIFY INSTITUTIONAL POLICY:]~~ It is unlikely that your child will be injured by being in this study. ~~This US federally funded study cannot offer compensation for research-related injury. If she is injured or gets sick from being in this study, please tell study staff immediately. We may be able to give her emergency treatment but you or your insurance company may be charged for this treatment.~~ **The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries.** You are not giving up any legal rights by signing this form. ***[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]*** **If your child becomes ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer your child for ongoing treatment for the injury, if needed. The study sponsor will be responsible for providing insurance to cover appropriate medical expenses for treatment of any such illness or injury, if the site does not already provide this insurance. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:**

- Any injury that happens because your child used other medicine during the study that you or your child did not tell us about.
- Any injury that happens because you or your child did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your or your child's part.

- Appendix VI, Sample Informed Consent Form (Screening, Enrollment, and Long-term Storage), "RESEARCH-RELATED INJURY" section:

~~[SITES TO SPECIFY INSTITUTIONAL POLICY:]~~ It is unlikely that you will be injured by being in this study. ~~This US federally funded study cannot offer compensation for research-related injury. If you are injured or get sick from being in this study, please tell study staff immediately. We may be able to give you emergency treatment but you or your insurance company may be charged for this treatment.~~ **The U.S. NIH does not have a mechanism to pay money or give other forms of financial compensation for research related injuries.** You are not giving up any legal rights by signing this form. ***[Sites to replace with their site-specific research-related injury institutional policy if they already provide clinical trials insurance:]*** **If you become ill or injured as a result of participation in this study, medical treatment for the adverse reaction or injury will be provided appropriately. The site staff will refer you for ongoing treatment for the injury, if needed. The study sponsor will be responsible for providing insurance to cover appropriate medical expenses for treatment of any such illness or injury, if the site does not already provide this insurance. An HIV infection that occurs during the course of the trial will not be considered an injury or illness caused by trial participation. The research site or sponsor is not responsible for any loss, injuries and/or damages that are caused by any of the following things:**

- Any injury that happens because you used other medicine during the study that you did not tell us about.
- Any injury that happens because you did not follow instructions given by the study doctor or nurse.
- Any injury that happens because of negligence on your part.

*The following revisions (#4-6) clarify/specify data management and documentation storage for the study's source data, including audio recordings:*

- 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 discussions files~~ (if applicable) **will be generated using audio recordings. 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) and audio files will be kept at the site in**

**the participant files. The qualitative data from MTN-034 will include three main source documents: audio files, transcripts, and notes taken during FGDs and IDIs.**

- Appendix V, Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-term Storage), "CONFIDENTIALITY" section, second paragraph, last sentence has been added to disclose how long the study's source data will be stored:

**[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: All original study documents that provide information about your child for this study will be kept for at least two years after either the vaginal ring is approved for use or research on the vaginal ring is stopped.]**

- Appendix VI, Sample Informed Consent Form (Screening, Enrollment, and Long-term Storage), "CONFIDENTIALITY" section, second paragraph, last sentence has been added to disclose how long the study's source data will be stored:

**[Sites to modify with their site-specific source documentation storage duration requirements if required by their IRBs/IECs: All original study documents that provide information about you for this study will be kept for at least two years after either the vaginal ring is approved for use or research on the vaginal ring is stopped.]**

- The following revisions to clarify/specify that dried blood spots (DBS) collected for PK will be collected only from participants taking Truvada were made to Section 7.4.2, Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68, Table 10, Laboratory-Blood, Section 7.4.3, Visit 23 – Week 72: Period 3 Product Use End/Early Termination Visit, Table 11, Laboratory-Blood, and Appendix I, Table of Visits and Study Procedures, Laboratory-Blood:

Dried blood spot (DBS) for PK (**Truvada users only**)

- The following revision was made to Section 7.9, Clinical Evaluations and Procedures, last bullet point in list of physical exam assessments:

● ~~Breasts (only applicable to 16-17 year olds)\*~~

- The following revision was made to the Protocol Cover Page to update the study IND# now that the study has been assigned one:

IND #: ~~FBD~~**139,598**

- The following revision was made to Appendix VI, Sample Informed Consent Form (Screening, Enrollment, and Long-term Storage), "What if I become pregnant?" section, second paragraph, last sentence, to remove mention of referring participants who become pregnant while on study product to MTN-016, the MTN Pregnancy Registry study, for consistency with the protocol assent and parental permission forms (Appendices IV and V, respectively) and given follow-up of pregnant participants would occur as part of the MTN-034 study:

~~[SITES TO INCLUDE/AMMEND THE FOLLOWING: We may also contact you about a study that collects information about pregnancy and children up to one year old.]~~

*Additional minor modifications include:*

- Section 1.5, Data Centers, Qualitative Data Center:

**Women's Global Health Imperative Program**  
RTI International  
351 California Street, Suite 500  
San Francisco, CA 94104 USA

12. Section 7.11, Specimen Management, first sentence:

Each study site will adhere to the standards of good clinical laboratory practice in accordance with **DAIDS Laboratory Policy** (<https://www.niaid.nih.gov/sites/default/files/laboratorypolicy1.pdf>) ~~current US DAIDS Laboratory Requirements~~ (<https://www.niaid.nih.gov/sites/default/files/gclp.pdf>), MTN-034 SSP Manual (<http://www.mtnstopshiv.org/studies>) and site SOPs for proper collection, processing, labeling, transport, and storage of specimens to standardize procedures.

13. Protocol Team Roster – Removals: Charlene Dezzutti.

14. Protocol Team Roster – Additions:

**Lisa C. Rohan, PhD**  
**MTN LC Co-Principal Investigator**  
University of Pittsburgh  
Magee-Womens Research Institute & Foundation  
204 Craft Avenue, Room B509  
Pittsburgh, PA 15213 USA  
Phone: 412-641-6108  
Fax: 412-641-6170  
Email: lrohan@mwri.magee.edu

**MTN Qualitative Data Management Center (QDMC)**

**Mary Kate Shapley-Quinn, MPH**  
**Project Coordinator and Data Manager**  
Women's Global Health Imperative Program  
RTI International  
351 California Street, Suite 500  
San Francisco, CA 94104 USA  
Phone: 415-848-1316  
Email: mshapley@rti.org

**Kim Woodhouse**  
**Program Manager**  
Women's Global Health Imperative Program  
RTI International  
351 California Street, Suite 500  
San Francisco, CA 94104 USA  
Phone: 415-848-1344  
Fax: 415-848-1330  
Email: kwoodhouse@rti.org

15. Protocol Team Roster – Updates:

John Mellors, MD  
~~Virology LC Director~~  
**MTN LC Co-Principal Investigator**  
University of Pittsburgh Physicians  
3550 Terrace Street, Suite 818  
Pittsburgh, PA 15261 USA  
Phone: 412-624-8512  
Fax: 412-383-7982  
Email: jwm1@pitt.edu

Ariane van der Straten, PhD, MPH  
**QDMC Director and BRWG Co-representative**  
**Women's Global Health Imperative Program**

RTI International  
351 California Street, Suite 500  
San Francisco, CA 94104 USA  
Phone: 415-848-1324  
Fax: 415-848-1330  
Email: ariane@rti.org

Sarah T. Roberts, PhD  
Research Analyst  
**Women's Global Health Imperative Program**  
RTI International  
351 California Street, Suite 500  
San Francisco, CA 94104 USA  
Phone: 415-848-1335  
Email: sroberts@rti.org

16. The Protocol Signature Page was updated to include Letter of Amendment #1 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-034 INVESTIGATOR SIGNATURE FORM**

**MTN-034**

**A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population**

**INVESTIGATOR SIGNATURE FORM**

Version 2.0; December 7, 2017  
Letter of Amendment #01; September 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 Sponsor:**

DAIDS (DAIDS Protocol ID: 12066)

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