LETTER OF AMENDMENT #03 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 December 7, 2017

DAIDS Protocol #12066
IND #139598

Date of Letter of Amendment: 30 June 2020

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. 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-034. The purpose of this LoA is to modify the sample size in the protocol and consent documents to reflect the difficult decision to forego resumption of participant enrollment at the sites because of COVID-19's impact on study activities. This LoA also adds a one-page study summary to the consent forms as per Common Rule requirements, allows retrospective HIV RNA testing on enrolled participants who acquire an HIV infection and modifies the grading criteria for blood pressure assessments on participants under 18 years old. This LoA also includes clarifications related to COVID-19's impact on study implementation per Clarification Memo #2, dated 27 May 2020, as follows: the content of the planned behavioral assessments may include questions related to the impact of the COVID-19 pandemic on the context of participants' HIV prevention and study product use; the overall study duration at study sites may be affected by COVID-19 closures; and changes to procedures may be implemented to mitigate potential hazards to participants or due to public health emergencies at the study sites.

Unless otherwise noted below, text to be deleted is noted by ~~strikethrough~~, 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

Enrollment of the MTN-034 study population was scheduled to be completed by April 30, 2020. With the emergence of the global pandemic of COVID-19 in mid-March of 2020, screening and enrollment activities for all MTN studies were suspended on March 18, 2020. Clinical Research Sites (CRS) continued to provide follow-up visits and study product to already enrolled participants, as feasible given national stay-at-home lockdown orders and COVID-19 driven limitations on in-person availability of clinical staffing.

Input from MTN-034 CRS indicated that completion of study procedures have been complicated by the need to initiate and maintain heightened infection control procedures, including ensuring the provision of masks, temperature and symptom screenings, physical distancing, minimizing in-person group activities, and the numbers of study participants and staff at the sites. These measures are likely to continue for as long as the COVID-19 pandemic remains a public health emergency in the areas surrounding the participating CRS, will likely continue to impact study operations, and would significantly impact the feasibility of successfully completing the long and complex study enrollment visits.

Although the MTN leadership lifted the network-wide pause in study enrollment on May 15, 2020, MTN-034 will not resume enrollment of new participants at its four CRS in Uganda, South Africa and Zimbabwe. The decision to forego resumption of participant enrollment was made to allow the MTN-034 CRS to continue to focus efforts on protecting safety of currently enrolled participants and staff, while maintaining strong retention and high-quality, youth-friendly implementation during the COVID-19 pandemic. With 247 of 300 expected participants already enrolled, including 85 of the target 100 participants under age 18, it was determined after considerable deliberations that the study will be able to yield sufficient data about the safety of the dapivirine vaginal ring, as well as oral PrEP, in adolescent girls and young women, and to do so within a shorter timeframe.

The following revisions (1-8) were made to the protocol-specified sample size to reflect the decision described above:

1. "Sample Size" section of Protocol Summary:

   ~~Approximately 300~~ **Two hundred and forty-seven** participants

2. Fourth sentence of third paragraph in Section 2.10, *Rationale for Study Design*:

   ~~Approximately 100~~ **Eighty-five** adolescent (16-17 years old) and ~~200~~ **162** young adult (18-21 years old) female participants ~~are expected to enroll~~ **were enrolled** in the trial~~, although more than 100 adolescents may enroll if sites are able to recruit from this age group with ease~~.

3. Second sentence of first paragraph, Table 13, and second paragraph in "Safety" sub-section of Section 10.4.1, *Primary Endpoints*:

   Table 13 shows the minimum detectable difference in rates of safety events assuming 80% power, α=0.05, a two-sided test based on Fisher's Exact Test, varying rates of safety events in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), **and** a sample size of **250** ~~300 participants and 10% loss to follow-up (a working sample size of 270)~~.

Table 13: Minimum Detectable Difference in Rates of Safety Outcomes Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
Rate of Safety Event in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
2%	~~9.1%~~ **5.8%**	~~7.6%~~ **4.8%**	~~6.4%~~ **4.1%**	~~5.0%~~ **3.2%**
5%	~~11.2%~~ **7.5%**	~~9.4%~~ **6.3%**	~~7.9%~~ **5.3%**	~~6.1%~~ **4.1%**
10%	~~13.4%~~ **9.2%**	~~11.2%~~ **7.7%**	~~9.5%~~ **6.5%**	~~7.3%~~ **5.0%**

If there is no intra-participant correlation for safety outcomes, the study will have 80% power to detect a minimum difference of ~~9.1%~~ **5.8%** to ~~13.4%~~ **9.2%** depending on the rate of the safety event in the treatment regimen with the lower rate. If the intra-participant correlation is moderately high (0.5), this minimum detectable difference ranges from ~~6.4%~~ **4.1%** to ~~9.5%~~ **6.5%**.

4. Second sentence and Table 14 in "Adherence" sub-section of Section 10.4.1, *Primary Endpoints*:

   Table 14 shows the minimum detectable difference in rates of ≥80% adherence assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ≥80% adherence in the treatment regimen with the lower rate, varying values of ρ (the intra-participant correlation), **and** a sample size of **250** ~~300, and 10% loss to follow-up (a working sample size of 270)~~.

   Table 14: Minimum Detectable Difference in Rates of ≥80% Adherence Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
≥80% Adherence Rate in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
60%	~~16.5%~~ **11.9%**	~~13.8%~~ **10.0%**	~~11.7%~~ **8.4%**	~~9.0%~~ **6.5%**
70%	~~14.9%~~ **10.8%**	~~11.5%~~ **9.0%**	~~9.8%~~ **7.6%**	~~7.5%~~ **5.9%**
80%	~~12.4%~~ **9.0%**	~~9.8%~~ **7.5%**	~~8.3%~~ **6.4%**	~~6.4%~~ **4.9%**
90%	~~8.6%~~ **6.3%**	~~7.6%~~ **5.3%**	~~6.4%~~ **4.5%**	~~4.9%~~ **3.5%**

5. Second sentence and Table 15 in "Acceptability" sub-section of Section 10.4.2, *Secondary Endpoints*:

   Table 15 below shows the minimum detectable difference in rates of acceptability of the two regimens assuming 80% power, α=0.05, a two-sided test based on the Normal approximation of the Binomial distribution, varying rates of ρ (intra-participant correlation), **and** a sample size of **250** ~~300, and 10% loss to follow-up (a working sample size of 270)~~.

Table 15: Minimum Detectable Difference in Rates of Acceptability Assuming 80% Power

	ρ			
	0.0	0.3	0.5	0.7
Acceptability Rate in Treatment Regimen with Lower Rate	Minimum Detectable Difference Between Treatment Regimens			
60%	~~16.5%~~ **11.9%**	~~13.8%~~ **10.0%**	~~11.7%~~ **8.4%**	~~9.0%~~ **6.5%**
70%	~~14.9%~~ **10.8%**	~~11.5%~~ **9.0%**	~~9.8%~~ **7.6%**	~~7.5%~~ **5.9%**
80%	~~12.4%~~ **9.0%**	~~9.8%~~ **7.5%**	~~8.3%~~ **6.4%**	~~6.4%~~ **4.9%**
90%	~~8.6%~~ **6.3%**	~~7.6%~~ **5.3%**	~~6.4%~~ **4.5%**	~~4.9%~~ **3.5%**

6. Second sentence of first paragraph in Section 10.5, *Participant Accrual, Follow-up and Retention*

   ~~Approximately 300~~ **Two hundred and forty-seven** participants ~~will be~~ **were** enrolled.

7. Fourth sentence in "Why is this study being done?" section of Appendix IV, *Sample Informed Assent Form*:

   ~~Three hundred~~ **Two hundred and forty-seven** healthy **adolescent and** young women who are 16 to 21 years old ~~will be~~ **were** enrolled in the study across **various sites in** South Africa, Uganda and Zimbabwe.

8. First sentence in "Who will be in this research study?" section of Appendices V-VI, *Sample Parent/Guardian Permission Form (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)* and *Sample Informed Consent Form (SCREENING, ENROLLMENT, and LONG-TERM STORAGE)*:

   ~~Three hundred~~ **Two hundred and forty-seven** healthy adolescent and young women who are 16 to 21 years old ~~will be~~ **were** enrolled in the study across various sites in South Africa, Uganda and Zimbabwe.

The following revisions (9-10) were made to add a one-page study summary to the assent and consent forms as per Common Rule requirements:

9. After the first paragraph of "Introduction" section in Appendices IV and VI, *Sample Informed Assent* and *Sample Informed Consent Form (Screening, Enrollment, and Long-Term Storage)*:

   Important things you should know:

   - **The study products in this research study each contain a different anti-HIV medication:**
     - **The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.**
     - **The oral tablet, Truvada, contains two drugs – 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.**

- **The purpose of this study is to find out if using the ring or the tablet is safe and well-tolerated by young women like you.**
- **You will use both the ring and the tablet. First, you will use one study product for six months, then the other study product for the next six months. You can choose to use either the ring or the tablet, or neither, during the final six months. You are randomly assigned to the study product you use for the first six months.**
- **You will be asked to complete up to twenty-four study visits, including up to four phone contacts. You will be in this study for about nineteen months.**
- **At some of the clinic visits, you will be asked to complete the following: a physical exam, a pelvic exam, blood draw, urine and vaginal fluid collection, several short interviews (and possibly one or more longer interviews or group discussions if you are selected), and you will be asked permission to access your medical records and contact your health care provider if necessary.**
- **Some common risks from the ring include: vaginal irritation, discharge and/or discomfort, and urinary tract infection. One serious but rare side effect seen with other vaginal rings is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria. To date this side effect has not been seen with the ring used in this study.**
- **Some common risks from the tablet include: nausea, abdominal pain, diarrhea, vomiting, passing gas, headache, dizziness, tiredness, and inability to sleep. More serious but rare side effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis.**
- **You will be using a study product that may prevent you from getting HIV if you use it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help to develop ways to prevent the spread of HIV in the future. You will receive testing for HIV and other sexually transmitted infections (STI), medical examinations, contraceptive counseling, and routine laboratory testing to check your overall health.**
- **Taking part in this research study is voluntary. You do not have to participate, and you can stop at any time.**
- **If you decide not to continue in this study, there are currently available methods to prevent sexually transmitted HIV: condom use during sex and/or oral pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide you with additional information about PrEP and PEP if you are interested.**

10. After the first paragraph of "Introduction" section in Appendices V, *Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-Term Storage)*:

<u>Important things you should know:</u>

- **The study products in this research study each contain a different anti-HIV medication:**
    - **The vaginal ring (VR) contains 25 mg of dapivirine (DPV). It is inserted in the vagina and worn continuously for approximately one month, to be replaced every month. We will refer to it in this document as the ring.**
    - **The oral tablet, Truvada, contains two drugs – 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF). It is taken once a day by mouth. We will refer to it in this document as the tablet.**

- **The purpose of this study is to find out if using the ring or the tablet is safe and well-tolerated by young women like your child.**
- **Your child will use both the ring and the tablet. First, she will use one study product for six months, then the other study product for the next six months. She can choose to use either the ring or the tablet, or neither, during the final six months. She is randomly assigned to which study product she uses for the first six months.**
- **Your child will be asked to complete up to twenty-four study visits, including up to four phone contacts. She will be in this study for about nineteen months.**
- **At some of the clinic visits, she will be asked to complete the following: a physical exam, a pelvic exam, blood draw, urine and vaginal fluid collection, several short interviews (and possibly one or more longer interviews or group discussions if she is selected), and she will be asked permission to access her medical records and contact her health care provider if necessary.**
- **Some common risks from the ring include: vaginal irritation, discharge and/or discomfort, and urinary tract infection. One serious but rare side effect seen with other vaginal rings is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacteria. To date this side effect has not been seen with the ring used in this study.**
- **Some common risks from the tablet include: nausea, abdominal pain, diarrhea, vomiting, passing gas, headache, dizziness, tiredness, and inability to sleep. More serious but rare side effects include: rash, liver problems, kidney problems, allergic reaction, and lactic acidosis.**
- **Your child will be using a study product that may prevent her from getting HIV if she uses it consistently, but neither study product can guarantee protection from HIV. Information learned from this study may help to develop ways to prevent the spread of HIV in the future. She will receive testing for HIV and other sexually transmitted infections (STI), medical examinations, contraceptive counseling, and routine laboratory testing to check her overall health.**
- **Taking part in this research study is voluntary. Your child does not have to participate, and she can stop at any time.**
- **If your child decides not to continue in this study, there are currently available methods to prevent sexually transmitted HIV: condom use during sex and/or oral pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP). Study staff can provide her with additional information about PrEP and PEP if she is interested.**

11. The following revision was made to the second bullet point of the third paragraph in Section 7.5.1, *Participants Who Become Infected with HIV,* to allow retrospective HIV RNA testing on enrolled participants who acquire an HIV infection to better understand the timing of infection:

    - HIV-1 genotyping will be performed on the stored plasma closest to the time of ~~confirmed~~ HIV-1 infection.
    - **HIV-1 RNA PCR or HIV-1 genotyping** ~~It~~ may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).

12. The following revision was made after the fourth paragraph of Section 8.3.1, *Adverse Events,* to modify the grading criteria for blood pressure assessments on participants under 18 years old:

    Protocol-specific grading scales will be used for the following AEs:

    - **Blood pressure abnormalities, <18 years of age**
        - **Grade 0: None**
        - **Grade 1: > 120/80 mmHg**
        - **Grade 2: ≥ 95th to < 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)**
        - **Grade 3: ≥ 99th percentile + 5 mmHg adjusted for age, height, and gender (systolic and/or diastolic)**
        - **Grade 4: Life-threatening consequences in a participant not previously diagnosed with hypertension (e.g., malignant hypertension) or hospitalization indicated**

    Note: Sites are not required to adjust the result by +5 mmHg per recommendation by the MTN-034 PSRT. Sites may consult the MTN-034 Protocol Safety Physician(s) for additional guidance.

13. Per Clarification Memo #2, dated 27 May 2020, the following clarification applies to the first sentence of the first paragraph and the second sentence of the second paragraph of Section 7.7, *Behavioral Evaluations*, and was added at the end of that section:

    Behavioral endpoints will be assessed via CASI/ACASI and/or CRFs with all participants.*****

    All IDIs and FGDs will be conducted by trained and experienced facilitators to gain further insight on the following behavioral issues:*****

    **** At Enrollment (for new participants) or at their next scheduled study visit (for already enrolled participants) and at one or more timepoints during the study, additional questions may be asked related to COVID-19's potential influence on the context of participants' HIV prevention and study product use, in order to explore the impact of the pandemic on study product adherence, acceptability, and preference.***

14. Per Clarification Memo #2, dated 27 May 2020, the following clarification applies to the "Study Duration" section of the Protocol Summary, to the first sentence of Section 4.4., *Time to Complete Accrual*, and to the first sentence of Section 10.5, *Participant Accrual, Follow-up and Retention*; and was added at the end of each section:

    Approximately 76 weeks of follow-up per participant with a projected accrual period of approximately 12 months at each site.*****

    Accrual will require approximately 12 months following site activation.*****

    The accrual period will be approximately 12 months at each site.*****

    **** 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 delays or pauses in enrolling participants at one or more research sites.

15. Per Clarification Memo #2, dated 27 May 2020, the following clarification applies to the first sentence of Section 13.1, *Institutional Review Boards/Ethics Committees*, and was added at the end of that section:

    Site investigators will make every effort to minimize risks to participants.*****

    **** Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes 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.] These changes 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.]***

16. Protocol Signature Page was updated to include Letter of Amendment #3; it is appended to the end of this document.

The above information, in addition to the changes from Letters of Amendment #1 and #2, will be incorporated into the next version of the protocol at a later time if it is amended.

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
Letter of Amendment #02; December 19, 2019
Letter of Amendment #03; June 30, 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: 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