

LETTER OF AMENDMENT #02 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: 19 December 2019

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 remove protocol references to the Kisumu Clinical Research Site (CRS) located in Kenya, as this CRS will no longer be involved in the MTN-034 study. The participants allocated to the Kisumu CRS have been distributed across the remaining four study sites. This LoA also removes the requirement to notify the Protocol Safety Review Team (PSRT) if study product is not retrieved within a week of a product use end visit (PUEV), clarifies protocol descriptions of the 25 mg dapivirine vaginal ring (DPV VR), updates information about DPV VR and Truvada studies, updates the DPV VR Investigator Brochure (IB) and Truvada tablet package insert versions, and updates the Protocol Team Roster.

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

Detailed Listing of Revisions

1. The following revisions were made to the List of Abbreviations and Acronyms to remove protocol references to the Kisumu CRS and the Kenyan Pharmacy and Poisons Board (PPB):

~~KEMRI — Kenyan Medical Research Institute~~

~~PPB — Pharmacy and Poisons Board (Kenya)~~

The following revisions (2-3) were made to remove protocol references to Kenya as one of the countries participating in the study:

2. Last sentence in “Why is this study being done?” section of Appendix IV, *Sample Informed Assent*:

Three hundred healthy young women who are 16 to 21 years old will be enrolled in the study across South Africa, ~~Kenya~~, Uganda and Zimbabwe.

3. “Who will be in this research study?” section of Appendix V, *Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-Term Storage)* and Appendix VI, *Sample Informed Consent Form (Screening, Enrollment, and Long-Term Storage)*:

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

The following revision was made to remove the protocol requirement to notify the PSRT if participants do not return study product within five business days of any of the three PUEVs. This revision does not affect the protocol requirement to notify the PSRT when product is not returned in a timely fashion in cases where safety is a concern (i.e., permanent product discontinuations and temporary product holds):

4. Last sentence of second paragraph in Section 6.5, *Retrieval of Study Product*:

~~If the study product is not retrieved within that timeframe, the MTN-034 PSRT must be informed.~~

Since determination of safety and effectiveness of a product is a regulatory responsibility and considering the DPV VR is currently under regulatory review, the protocol language regarding safety and effectiveness of the DPV VR has been modified. Therefore, the following revisions (5-13) were made to replace all protocol descriptions of the DPV VR as “safe” and “effective” with more precise terms (e.g., “well-tolerated”, “statistically significant reduction in the risk of HIV-1 infection”):

5. Second sentence of fifth paragraph in Section 2.1, *Microbicides and oral PrEP in HIV/AIDS Prevention*:

Both studies found the VR to be ~~safe and effective in reducing~~ **well-tolerated, and both studies showed a statistically significant reduction in the risk of HIV-1 infection** in healthy female adults in sub-Saharan Africa when used for one month and replaced monthly.^{11,12}

6. First sentence of first paragraph in “Safety” sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

Across all clinical trials conducted in healthy participants evaluating multiple ring configurations ~~formulations~~, the dapivirine VR was generally ~~safe and~~ well-tolerated.²²

7. First sentence of seventh paragraph in “Extended Safety and Efficacy” sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

The dapivirine ring was ~~safe and effective in preventing~~ **well-tolerated and led to a statistically significant reduction in the risk of HIV-1** infection in both ASPIRE and The Ring Study.

8. Fourth sentence of eighth paragraph in “Extended Safety and Efficacy” sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

The study ~~will evaluate~~ **evaluated** the safety of and participant adherence to the dapivirine (~~25 mg~~) VR in the context of an open-label extension trial, reflecting a transition to a more real-world type of product use where the participants know they are getting an active product that has been shown to be ~~safe and effective~~ **well-tolerated and to provide a statistically significant reduction in the risk of HIV-1 infection** when used as indicated.

9. Last sentence of third paragraph in Section 2.10, *Rationale for Study Design*:

It is important to note that there will not be a washout period between study product use periods as withholding an ~~effective~~ HIV preventative agent from this at-risk population during the trial would be unethical.

10. First sentence of first paragraph and second sentence of second paragraph in Section 13.4.2, *Benefits*:

Given that the dapivirine VR as tested in MTN-020 (ASPIRE), **MTN-025 (HOPE)**, and IPM 027 (The Ring Study) **and IPM 032 (DREAM)** was found to be **well-tolerated safe and effective**, participants in MTN-034 will experience the direct benefit of using a product that has been found to be ~~safe and effective in preventing HIV acquisition and will be~~ **an HIV-1 prevention product currently being** considered for potential regulatory approval.

Specifically, information learned in this study may help to understand issues important for broader implementation of the dapivirine ring and PrEP and/or for the development of other ~~safe and effective~~ interventions to prevent HIV-1 acquisition in adolescent and young adult women.

11. Fifth and sixth sentences in Section 13.7.2, *Children*:

Both products being used in this study have been shown to be ~~safe and effective~~ **well-tolerated and to provide a statistically significant reduction in the risk of HIV-1 infection** in adults **when used as instructed**. However, ~~as of December 2016, dapivirine was not approved in the countries where the implementation of this trial is planned, and though FTC/TDF for oral PrEP was approved in two of the trial countries, South Africa and Kenya, it~~ **dapivirine is still under consideration for potential regulatory approval as an HIV-1 prevention product, and Truvada for oral PrEP has**

not yet been made widely accessible in **the countries where the study is being implemented** either country.

12. First sentence of the “Why is this Study Being Done?” section in Appendix IV, *Sample Informed Assent*:

A vaginal ring (which contains a drug called dapivirine) and an oral tablet (which is called Truvada) ~~have been proven to be safe for use~~ **were well-tolerated when used** by adolescents and adults, and ~~to protect against~~ **reduced the risk of HIV-1 infection** when used consistently by people 18 years and older.

13. Third, fourth, and after the last sentence of second paragraph in the “Why is this research being done?” section of Appendix V, *Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-Term Storage)* and Appendix VI, *Sample Informed Consent Form (Screening, Enrollment, and Long-Term Storage)*:

The dapivirine **vaginal** ring was tested and found to be ~~safe~~ **well-tolerated when used** ~~for use~~ by adolescent (15-17 years old) and adult (18 years and older) women. It was also found to ~~be effective in preventing HIV~~ **reduce the risk of HIV-1 infection** in women ages 22-45 when used consistently.

The ring has not yet been approved as an HIV-1 prevention product by regulatory agencies like the Food and Drug Administration (FDA) or European Medicines Agency.

The following revisions (14-26) were made to update information about DPV VR and Truvada studies in the study protocol, including updating the DPV VR risk language so it better aligns with DPV VR risk language in the current DPV VR IB and incorporating recently disseminated results from the MTN-025 (HIV Open-label Prevention Extension [HOPE]), IPM 032 (Dapivirine Ring Extended Access and Monitoring [DREAM]) and HPTN 082 studies:

14. Last sentence of first paragraph in Section 2.2.2, *FTC/TDF Tablet*:

Truvada® for oral PrEP ~~was also~~ **has been** approved for use by adults at high risk of sexually acquiring HIV-1 infection in ~~both~~ **a number of other countries, including South Africa, Zimbabwe, and Uganda; due to the high cost of Truvada®, the Ugandan Ministry of Health has recommended the use of the TDF/lamivudine (3TC) (300/300 mg) tablet for PrEP instead.** ~~and Kenya, first by South Africa’s Medicines Control Council (MCC) in November 2015, shortly followed by Kenya’s Pharmacy and Poisons Board (PPB) in December 2015.~~

15. First sentence of first paragraph, first and fourth bullet points, and first sentence of second paragraph in Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

To date, a total of ~~29~~ **31** Phase 1 and Phase 1/2 clinical trials of dapivirine have been ~~conducted, with all but two~~ completed:²²

- ~~Eight~~ **Ten** trials of dapivirine VRs (containing 25 mg loads); a total of ~~298~~ **503** participants were assigned to receive dapivirine VRs

- Two trials of dapivirine vaginal film; a total of **2574** women were assigned to receive dapivirine vaginal film

Additionally, ~~two recently~~ **Two** completed Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), evaluated long-term safety and efficacy of the 25 mg dapivirine vaginal Ring-004, in which the VR was replaced with a new VR after approximately 28 days of use.

16. After the last sentence of second paragraph in Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

Two Phase 3B open-label extension trials, IPM 032 (DREAM) and MTN-025 (HOPE), offering the extended use of the VR to former participants of The Ring Study and ASPIRE, respectively, have also been completed. A total of 2309 participants were enrolled between the two Phase 3B studies, including 978 assigned to the placebo rings in the Phase 3 trials.²²

To date, a total of 4100 adult women between 18 and 65 years of age have been exposed to the dapivirine VR across the clinical development program's completed Phase 1-3B studies.²²

17. Second sentence of fifth paragraph in "Safety" sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

It has been evaluated in ~~five~~ **eight** completed **Phase 1 and Phase 2** clinical trials.²²

18. Third sentence of fifth paragraph and third sentence of seventh paragraph in "Extended Safety and Efficacy" sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

In pre-defined as-randomized subgroup analyses, HIV protection differed significantly by age, with a 61% reduced risk of HIV for women ≥ 25 years (**95%** [CI: 32%, -77%, } $p < 0.001$), and 10% reduced risk for women < 25 years (**95%** CI: -41%, -43%, } $p = 0.64$).

~~Two open label studies are currently under way to evaluate~~ **were recently completed, evaluating** the VR's effectiveness in a more real-world setting as the VR moves through the marketing approval process.

19. First and fifth sentences of eighth paragraph in "Extended Safety and Efficacy" sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

MTN-025, the HIV Open-label Prevention Extension (HOPE) trial, ~~is~~ **was** a multi-site, open-label, randomized, Phase 3b trial ~~currently being~~ implemented in the ASPIRE trial research sites.³⁹

~~The HOPE sample size will be contingent upon how many former ASPIRE participants are interested in enrolling,~~ **are study enrolled 1456 former ASPIRE participants who were HIV- negative and otherwise eligible to enroll. As with ASPIRE, the HOPE study found no significant safety concerns with the ring, and ring use adherence was higher in HOPE. Furthermore, though the HOPE study lacked a comparison placebo group, HIV-1 incidence was lower than expected by weighted bootstrap**

sampling of the placebo arm of ASPIRE (matched by site, age, and presence of a curable STI at baseline).

Product-related AEs were minimal and similar in frequency and severity as those observed in ASPIRE, with no SAEs related to ring use. At baseline, 1342 participants (92%) accepted the VR, and ring uptake remained high throughout the study: 90%, 89%, 87%, 83%, and 79% at Months 1, 2, 3, 6, and 9. Most (86%) returned rings had residual dapivirine levels consistent with some use during the prior month (>0.9 mg released). A total of 35 HIV-1 infections were observed among enrolled participants between July 2016 and August 2018 for an observed incidence of 2.7 per 100 person-years (95% CI: 1.9-3.8) among all women in HOPE, regardless of ring acceptance or use. Expected HIV-1 incidence was 4.4 per 100 person-years (95% CI: 3.2-5.8) in the absence of access to the ring; an incidence of ≤ 2.7 would be expected to occur in fewer than 33 in 10,000 (0.33%) samplings. Lastly, no clear resistance pathway for resistance-associated mutations potentially selected by DPV was identified based on the pattern of NNRTI mutations observed among the 35 HOPE participants who acquired an HIV infection during the study.

20. Last paragraph in “Extended Safety and Efficacy” sub-section of Section 2.7.1, *Clinical Studies of Dapivirine Vaginal Rings*:

IPM 032, the Dapivirine Ring Extended Access and Monitoring (DREAM) study, is ~~is~~ **was** a multi-site, open-label follow-on trial to The Ring Study ~~currently being implemented in six of the IPM 027 sites.~~⁴⁰ ~~Approximately 1700~~ **In total, 941** eligible HIV-uninfected former Ring Study participants, ~~as well as ring-naïve women aged 18-25, will~~ **will** receive the same VR used in The Ring Study. Like the HOPE study, DREAM study participants ~~will be~~ **were** asked to use the VR for a total period of 12 months, replacing it monthly, and to attend monthly study follow-up visits for the first 3 months and quarterly thereafter. In addition to offering former Ring Study participants access to the VR and evaluating the safety of and participant adherence to the dapivirine VR in the context of an open-label extension trial, the DREAM study ~~will~~ **will** also explore when, how and why young women used the ring, as well as how adherence may ~~have affected~~ **have** affected the VR's efficacy and ways to support effective VR use.

The ring was found to be well-tolerated in DREAM with a safety profile similar to The Ring Study. Most (95%) DREAM participants had returned rings with residual dapivirine levels which showed they had used the ring at least some of the time (ranging from intermittent to consistent use), up from 83% in The Ring Study. From July 2016 to November 2018, an HIV-1 incidence of 1.6% was observed, compared to an incidence rate of 4.3% in a simulated placebo group based on data from participants with similar characteristics in the placebo arm of The Ring Study, suggesting an estimated 63% reduction in HIV-1 risk for women who used the ring.

21. Second sentence of first paragraph in “Effectiveness of Truvada as PrEP in Studies that Enrolled Women” sub-section of Section 2.7.2, *Clinical Studies of FTC/TDF Tablet (Truvada)*:

In late 2015, ~~both~~ the South African **Medicines Control Council (MCC)** ~~MCC~~ and the Kenyan ~~PPB~~ also approved Truvada® for use as oral PrEP by adults at high risk of

sexually acquiring HIV-1 infection. **National drug regulatory bodies in Zimbabwe and Uganda followed suit in March 2017 and December 2017, respectively.**²⁵

22. Paragraph labeled “HPTN 082” in “Uptake, adherence and efficacy of open label FTC/TDF in African women” sub-section of Section 2.7.2, *Clinical Studies of FTC/TDF Tablet (Truvada®)*:

HPTN 082 ~~is~~ **was** a Phase IV, randomized, open-label, multi-site prospective study that ~~will~~ **assessed** PrEP acceptance and adherence among HIV-uninfected young women ages 16-25 years in South Africa (Cape Town and Johannesburg) and Harare, Zimbabwe. All participants ~~will be~~ **were** offered once-daily oral FTC 200 mg/TDF 300 mg. The study ~~will~~ **recruited 427** ~~approximately 400~~ young women who ~~either~~ **adopted** PrEP at enrollment and ~~up to 200 young women who are eligible and or were~~ **interested** in PrEP but ~~declined~~ **PrEP** at enrollment; ~~these latter participants, who will~~ **continued** to be offered PrEP after enrollment. All women who ~~accepted~~ **PrEP** ~~will be~~ **were** randomized 1:1 to receive enhanced adherence counseling based on feedback from observed drug levels or standard adherence support. A subset of up to ~25 women per site (maximum 75), ~~will~~ **participated** in qualitative assessments of facilitators and barriers for PrEP acceptance, adherence and continuation. The primary study objectives ~~are~~ **were** to assess the proportion and characteristics of young HIV-uninfected women who ~~accepted~~ **vs. declined** PrEP at enrollment, and to assess the difference in PrEP adherence using counseling based on drug levels from the 4- and 8-week visits in participants randomized to the enhanced versus standard arms. Participants ~~will be~~ **were** followed for 12 months. The trial began enrollment in October 2016 **and completed follow-up in October 2018.**

Most (95%) enrolled participants initiated PrEP either with standard or enhanced adherence support, and most (84%) participants who returned for follow up had detectable levels of tenofovir diphosphate (TFV-DP) in their blood according to dried blood spot (DBS) analyses. Among these participants, 25% had TFV-DP levels suggesting “high adherence.” At six- and twelve-month follow-up visits, investigators found that participants with detectable levels of TFV-DP declined to 57% and 31%, respectively. Only 9% of young women had TFV-DP levels associated with high adherence at 12 months. Overall, four women acquired HIV during the study, all of whom had undetectable drug levels in their blood, suggesting limited adherence to PrEP. Investigators saw no difference in drug levels between the two randomized groups at three, six or twelve months, indicating that drug level feedback did not improve PrEP adherence. The preliminary results suggest that tailored, evidence-based adherence support strategies may be needed to durably engage young African women in consistent PrEP use, and that HIV prevention methods that do not rely on daily adherence may be advantageous in this population.⁵⁷

23. Last sentence in paragraph labeled “IMPAACT 2009” in “Uptake, adherence and efficacy of open label FTC/TDF in African women” sub-section of Section 2.7.2, *Clinical Studies of FTC/TDF Tablet (Truvada®)*:

~~As of Q4 2017, the~~ **The** trial is in development and sites ~~have been selected~~ **currently enrolling** in Zimbabwe, Malawi, Uganda and South Africa.⁵⁹

24. First sentence of the first paragraph, second sentence of the second paragraph, and last sentence of the third paragraph in the “Dapivirine” sub-section of Section 13.4.1, *Risks*:

Use of the study VR may lead to ~~vaginal symptoms, including irritation, increased discharge, and discomfort (including with vaginal intercourse)~~ **urinary tract infections, vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain. Less common side effects include: cervicitis, cystitis, vaginal odor, cervix erythema, cervix ecchymosis, cervix edema, cervical discharge, vulvovaginal pain/discomfort, pelvic discomfort, vaginal/uterine cervical erosion, genital itching/discomfort, dysuria, pollakiuria, bladder pain, abdominal pain/discomfort, suprapubic pain, application site pain/discomfort, and vaginal laceration.**

No safety concerns were noted in ~~DPV~~ **dapivirine** VR users as compared to placebo VR users. **There were no new safety concerns noted in the two dapivirine VR open-label extension trials, MTN-025 (HOPE) and IPM 032 (DREAM), which enrolled a total of 2309 women, and results were reported in July 2019 and June 2019, respectively.**

Clinical relevance has yet to be established, **however, as no clear resistance pathway has emerged. All NNRTI mutations observed in women using dapivirine VRs have also been observed in women using placebo rings, and it is unclear if the observed mutations were transmitted or arose due to dapivirine selective pressure given the increasing prevalence of NNRTI resistance mutations in the study communities and the absence of data on the transmitting partner’s virologic profile.**

25. After the fifth bullet point of the “What are the Risks of the Study?” section in Appendix IV, *Sample Informed Assent*:

Some women who used the vaginal rings in other studies have had:

- ~~Discharge from the vagina, some pain, burning or itchiness in the vagina, or vaginal bleeding in between usual periods~~ **urinary tract infections.**

Less common side effects included:

- **Cervical irritation, bruising, swelling, inflammation, wearing, and discharge; bladder pain and inflammation; vaginal odor, itching, tearing, and discomfort; pelvic and abdominal pain and discomfort; and problems urinating.**

26. After the second bullet point in the “Risks of the Vaginal Ring” section of Appendix V, *Sample Parent/Guardian Permission Form (Screening, Enrollment, and Long-Term Storage)* and Appendix VI, *Sample Informed Consent Form (Screening, Enrollment, and Long-Term Storage)*:

- ~~Urinary tract infections~~ ~~Vaginal bleeding in between their usual periods~~

Less common side effects included:

- **Cervical irritation, bruising, swelling, inflammation, wearing, and discharge; bladder pain and inflammation; vaginal odor, itching, tearing, and discomfort; pelvic and abdominal pain and discomfort; and problems urinating.**

27. Protocol references to the DPV VR IB were updated to the most current version dated 11 November 2019.
28. Protocol references to the Truvada Package Insert were updated to the most current version dated May 2018.
29. Protocol Team Roster – Deletions: Nelly Mugo, Felix Mhlanga, Gonasagrie Nair (as Site Investigator of Record only, not as Protocol Chair) and Renee Ridzon.
30. Protocol Team Roster – Additions:

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31. Protocol Team Roster – Corrections:

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32. Protocol Signature Page was updated to include Letter of Amendment #02; it 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.

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

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