

LETTER OF AMENDMENT #01 TO:

MTN-042

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

Version 1.0, dated April 16, 2019

**DAIDS Protocol #38544
IND #139598**

Date of Letter of Amendment: 17 December 2019

Site Instruction

The following information impacts the MTN-042 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-042. The purpose of this LoA is to incorporate several recommendations stemming from the US Food and Drug Administration (FDA) review of the study protocol, including clarifications to eligibility criteria, modifications to reporting criteria, product hold criteria and serum creatinine assessment frequency, and specification of blood volume amounts drawn from infants. This LoA also clarifies HIV testing procedures for infants, specifies which visit procedures will be the Early Termination Visit procedures for the infants, reduces the frequency of social benefits behavioral assessments, adds explicit mention of mental health assessments to the protocol and consent forms, clarifies the study hypotheses, clarifies protocol descriptions of the 25 mg dapivirine vaginal ring (DPV VR), updates information about DPV VR studies, makes other minor edits to correct additional inconsistencies, omissions and errors in the protocol and consent forms, 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 revision was made to exclusion criterion #5j in Section 5.3, *Exclusion Criteria*, to include explicit mention of premature rupture of membranes (term or preterm)

and all forms of abnormal placentation as examples of obstetrical complications that would lead to exclusion from the study, as recommended by US FDA reviewers:

- j. At Enrollment, as determined by the IoR/designee, has any significant obstetrical complication (**e.g., premature rupture of membranes, any abnormal placentation**) or uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease that would make study participation unsafe.

The following revisions (2-3) were made to mention explicitly the reporting criteria for HIV acquisition and to clarify the reporting criteria for maternal AEs related to fetal losses as recommended by US FDA reviewers:

2. After the last bullet point of first bullet point list in Section 8.3.1, *Adverse Events*:

- **HIV acquisition**
 - **All instances of HIV acquisition will be reported by sites on HIV Confirmatory Results CRFs to the SDMC and will be considered during safety reviews conducted by the SDMC, the DAIDS MO, the NICHD MO, PSRT, and IRP.**

3. Last bullet point of first bullet point list in Section 8.3.1, *Adverse Events*:

- Fetal losses (e.g., spontaneous abortions, spontaneous fetal deaths, stillbirths);
 - **However, untoward maternal conditions that either result in or result from fetal losses are will be reported as reproductive system AEs.**

The following revisions (4-5) were made to modify the study product hold criteria for vaginal bleeding and to clarify the same for chorioamnionitis and cervicitis as recommended by US FDA reviewers:

4. Section 9.5, *Other Clinical Findings*, after “STI/RTI requiring treatment” sub-section:

Management of vaginal bleeding and chorioamnionitis events observed at scheduled or interim visits for all participants will be in accordance with the following:

≥ Grade 2 genital bleeding

- **Temporarily hold study product.**
- **Perform naked eye evaluation.**
- **If determined to be due to deep epithelial disruption, refer to guidelines below; otherwise study product will be permanently discontinued.**

≥ Grade 2 chorioamnionitis

- **Participants who develop Grade 2 or higher chorioamnionitis will be referred for delivery per local standard of care; therefore, study product will be permanently discontinued.**

5. Section 9.5, *Other Clinical Findings*, after “Generalized erythema or severe edema” sub-section:

Unexpected **Grade 1** genital bleeding

- Continue study product use (at study clinician’s discretion).
- Perform naked eye evaluation.
- If determined to be due to deep epithelial disruption, refer to guidelines above; otherwise continue study product use.

Cervicitis (including findings on exam such as inflammation and/or friability)

- Temporarily hold study product.
- Evaluate for GC/CT; consider syndromic management, pending results of testing and per clinician discretion.
- If GC/CT detected, provide or prescribe treatment.
- Reevaluate in 3-5 days. If all symptoms and signs are resolved at that time, **regardless of etiology**, resume study product use.
- **If unresolved at 3-5 days, continue temporary product hold, consult with PSRT regarding permanent discontinuation, and provide care per local standard.**

The following revisions (6-8) were made to increase the frequency of required serum creatinine assessments for mothers in the Truvada arm as recommended by US FDA reviewers. The reviewers recommended testing of serum creatinine at Week 4 and every 12 weeks thereafter. The protocol team elected to perform the testing for both study arms to avoid biasing AE assessments for one arm:

6. “Laboratory-Blood” section of Table 5: Bi-weekly Visits After 36th Week of Gestation in Section 7.4.2, *Bi-weekly Visits After 36th Week of Gestation*:

- **Creatinine (Cohort 1 only) ▲**
- **Creatinine (Cohorts 2-4)***

7. “Laboratory-Blood” section of Table 7: 4-week Visit(s) (Cohorts 2-4) in Section 7.4.4, *4-week Visit(s) (Cohorts 2-4)*:

- Creatinine ~~π ∇ (Truvada group only)~~

π Required at 1st 4-week Visit and every 12 weeks thereafter

8. “Laboratory-Blood” section of table in Appendix I, *Table of Visits and Study Procedures – Mothers*:

	Visit 1 SCR	Visit 2 ENR	Phone Contacts Prior to Pregnancy Outcome	Cohorts 2-4 only		Bi- weekly Visits After 36 th Week	PPO Visit	1-week PPO Phone Contact	6- week PPO Visit/ SEV/ Early SEV
				2- week Visit	4- week Visit(s)				
Creatinine (Cohort 1 only)	X	X				▲	*		X

Creatinine (Cohorts 2-4) (Required at 4-week Visit(s) for Truvada group only)	X	X		*	π ∇	*	*		X
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▲ Required at second Bi-weekly Visit (as needed) and if indicated at all others
 π Required at 1st 4-week Visit and every 12 weeks thereafter

The following addition was made to specify the maximum total amounts of blood to be drawn from the infants for research purposes throughout the study and to note that blood sampling volumes will comply with US National Institutes of Health (NIH) guidelines for limits on blood drawn for research purposes, as recommended by US FDA reviewers:

9. After “Designated Laboratory” sub-section of Section 7.12, *Laboratory Evaluations*:

Infant blood draw volume amounts planned for this study fall within the limits recommended by the U.S. National Institutes of Health (NIH) Guidelines for Limits on Blood Drawn for Research Purposes for pediatric patients: ≤ 5 mL/kg in a single day and ≤ 9.5 mL/kg over any eight-week period.⁷⁸ The maximum amount required to be drawn for research purposes from infants in the Truvada arm is 5 mL over 12 months of study participation (with ≤ 3 mL in a single day and ≤ 5 mL in any given eight-week period). The maximum amount required to be drawn for research purposes from infants in the DPV VR arm is 4 mL over 12 months of study participation (with ≤ 2 mL in a single day and ≤ 4 mL in any given eight-week period). See Table 15 below for a summary of infant blood volumes to be drawn for research purposes by clinic visit and by study arm. Additional blood may be drawn if clinically indicated, including: HIV testing (3-4 mL); creatinine, AST and ALT (1-2 mL); and CBC (1 mL). In instances of clinical need, it is the responsibility of the infant’s attending physician to determine if phlebotomy in excess of the stated limits may be permitted, particularly for patients with significant anemia or compromised cardiac output.

Table 1. Infant Blood Draw Volumes by Study Arm and by Clinic Visit

Clinic Visit	Truvada Group	DPV VR Group
PPO Visit	3 mL	2 mL
6-week PPO Visit	2 mL	2 mL
6-month PPO Visit	0 mL	0 mL
12-month PPO Visit	0 mL	0 mL
TOTAL	5 mL	4 mL

The following revisions (10-12) were made to reduce the frequency of required serum creatinine assessments for infants in the Truvada arm. There is no justification to support creatinine assessments months after tenofovir exposure given the additional risk of blood draws for infants, and thus serum creatinine assessment procedures at the 6-month and 12-month PPO Visits will no longer be required unless clinically indicated. The protocol team also elected to perform the testing at the PPO and 6-week PPO Visits for both study arms to provide comparison data for the Truvada arm:

10. “Laboratory-Blood” section of Table 9: PPO Visit – Infants in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*, and Table 13: 6-week PPO Visit – Infants in Section 7.5.3, *6-week PPO/Study Exit Visit (SEV)/Early SEV*:

- Creatinine~~‡~~

~~‡ Required for Truvada group and if indicated for DPV group~~

11. “Laboratory-Blood” section of Table 14: Semi-annual PPO Visits/Early SEV in Section 7.6, *Semi-annual PPO Visits/Early SEV for Infants*:

- Creatinine~~‡~~ *

~~‡ Required for Truvada group and if indicated for DPV group~~

12. “Laboratory-Blood” section of table in Appendix II, *Table of Visits and Study Procedures – Infants*:

	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit	6-month PPO Visit	12-month PPO Visit/ Early SEV
Creatinine	‡ X		‡ X	‡ *	‡ *

~~‡ = Required for Truvada group and if indicated for DPV group~~

The following revisions (13-14) were made to clarify that HIV testing procedures will be performed both on infants born to HIV-positive mothers and on infants whose mothers seroconvert after giving birth, and to specify which procedures will be performed on infants of HIV-positive mothers and which will be performed on HIV-positive infants:

13. Fourth paragraph in Section 7.7.1, *Participants Who Become Infected with HIV*:

Upon delivery of a live infant by an HIV-infected participant, **or upon HIV seroconversion of a participant between the birth of her infant and her infant’s first birthday (whether found via study testing or report from external testing)**, the following procedures are performed on the infant if consented to by the participant:

- Infant HIV-1 testing will be performed at the PPO Visit or as soon as possible after delivery **for infants born to HIV-positive participants. For infants whose mothers seroconverted after they were born, HIV-1 testing will be performed as soon as possible after discovery of the mother’s HIV-positive status.** Infant HIV-1 testing (including confirmation of HIV infection) **will be done per local standard of care and** may occur at a scheduled visit or an interim visit.

The following procedures are performed on HIV-positive infants if consented to by the participant:

- ~~Repeat~~ **Immediately following confirmation of HIV infection, perform plasma collection, CD4+ T cell count, HIV-1 RNA PCR test, and ~~de~~ HIV-1 genotyping.** ~~HIV-~~

~~1 genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).~~

- Facilitate rapid referral of the infant for appropriate further management including necessary blood tests, urgent ART initiation, and adherence counselling and follow up for the mother/guardian.
- **At all subsequent scheduled clinic visits until the infant is one year old, perform Pplasma collection, CD4+ T cell count and HIV-1 RNA PCR. HIV-1 genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).** ~~will be performed at the next scheduled clinic visit and every three months thereafter for a minimum of twelve months.~~

14. Second sentence of second paragraph in “What if I become infected with HIV and my baby becomes infected?” section of Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) – INFANT:*

If your baby becomes HIV-positive and you agree to the procedures, your baby will have visits every three months for at least 12 months for additional tests during their regularly scheduled study visits.

The following revisions (15-16) were made to clarify the reporting criteria for vaginal discharge and vaginal bleeding, and to add the AE grading criteria for infant AEs related to fever and to creatinine:

15. After the last bullet point of first bullet point list in Section 8.3.1, *Adverse Events:*

- **Physiologic discharge associated with pregnancy.**
- **Vaginal bleeding that is judged by the clinician to be within the range normally anticipated in the postnatal period.**

16. After last set of bullet points in Section 8.3.1, *Adverse Events:*

- **Axillary measured fever**
 - **Grade 0: None**
 - **Grade 1: 99.3°F to <100.4°F (37.4°C to <38°C)**
 - **Grade 2: 100.4°F to <101.7°F (38°C to <38.7°C)**
 - **Grade 3: 101.7°F to <102.9°F (38.7°C to <39.4°C)**
 - **Grade 4: ≥102.9°F (≥39.4°C)**
- **Creatinine (neonates 0-28 days old)**
 - **Grade 0: None**
 - **Grade 1: 1.1 mg/dL to <1.6 mg/dL**
 - **Grade 2: 1.6 mg/dL to <2.1 mg/dL**
 - **Grade 3: 2.1 mg/dL to 3.0 mg/dL**
 - **Grade 4: >3.0 mg/dL**
- **Creatinine (infants >28 days old)**
 - **Grade 0: None**
 - **Grade 1: 0.5 mg/dL to <0.7 mg/dL**
 - **Grade 2: 0.7 mg/dL to <0.9 mg/dL**

- **Grade 3: 0.9 mg/dL to 1.2 mg/dL**
- **Grade 4: >1.2 mg/dL**

The following revisions (17-20) were made to specify that the Semi-annual Post-Pregnancy Outcome (PPO) Visit procedures will be the Early Termination Visit procedures for the infants:

17. Title of Section 7.6, *Semi-annual PPO Visits for Infants* and table header of Table 14: Semi-annual PPO Visits in the same section:

Semi-annual PPO Visits/**Early SEV** for Infants

18. Title of Table 14: Semi-annual PPO Visits in Section 7.6, *Semi-annual PPO Visits for Infants*:

Semi-annual PPO Visits/**Early SEV**

19. At the end of the paragraph in Section 7.6, *Semi-annual PPO Visits for Infants*:

This set of visit procedures will also be performed as the Early SEV for infants who are withdrawn from the study for any reason, if their mothers are willing to bring them in for a final study visit.

20. Table header in Appendix II, *Table of Visits and Study Procedures – Infants*:

12-month PPO Visit/**Early SEV**

The following revisions (21-23) were made to reduce the frequency of administration of the social harms behavioral assessment to once per participant, at study exit:

21. “Behavioral/Counseling” section of Table 7: 4-week Visit(s) (Cohorts 2-4) in Section 7.4.4, *4-week Visit(s) (Cohorts 2-4)*:

- Social harms/~~benefits~~ assessment ϕ

22. “Behavioral/Counseling” section of Table 12: 6-week PPO/SEV/Early SEV – Mothers in Section 7.5.3, *6-week PPO/SEV/Early SEV – Mothers*:

- Social harms/~~benefits~~ assessment
- **Social benefits assessment**

23. “Behavioral/Counseling” section of table in Appendix I, *Table of Visits and Study Procedures – Mothers*:

				Cohorts 2-4 only					
	Visit 1 SCR	Visit 2 ENR	Phone Contacts Prior to Pregnancy Outcome	2-week Visit	4-week Visit(s)	Bi-weekly Visits After 36 th Week	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit/SEV/Early SEV

Social harms/benefits assessment					φ				X
Social benefits assessment									X

The following revisions (24-25) were made to include explicit mention of mental health assessments for pre- and postpartum participants in this study’s protocol and consent form documents:

24. After the last sentence in Section 7.10, *Counseling*:

Participants will be monitored for symptoms of depression throughout their participation in the study. A validated depression scale designed for use with pregnant and postpartum women will be administered in the antenatal period and in the postpartum period. Participants will be referred to additional counseling and/or mental health services if clinically indicated.

25. After the first sentence of the first bullet point in the “What procedures will be done for this study?” section of Appendices V-VIII, Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), MOTHER – COHORTS 1-4:

We will ask questions about your thoughts and feelings and your mood.

The following revisions (26-28) were made to the study hypotheses to clarify that participants will only be using one of the study products, not both:

26. Study Hypotheses section in Protocol Summary:

- Daily use of Truvada oral tablet ~~and or~~ dapivirine (DPV) vaginal matrix ring (25 mg) inserted once every 4 weeks will ~~both~~ be generally safe and well-tolerated by the participants and their fetuses/infants.
- Participants who use Truvada oral tablet daily ~~and or~~ insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

27. Second sentence of first paragraph in Section 2.9, *Rationale for Study Design*:

This study will further elucidate safety during pregnancy by testing the hypothesis that the administration of ~~the DPV VR and Truvada~~ **either study product** will ~~both~~ be safe and well-tolerated by women and their fetuses/infants...

28. Section 10.3, *Primary Study Hypotheses*:

- It is hypothesized that daily use of Truvada oral tablet ~~and or~~ DPV vaginal matrix ring (25 mg) inserted once every 4 weeks will ~~both~~ be generally safe and well-tolerated by the participants and their fetuses/infants.

- It is hypothesized that participants who use Truvada oral tablet daily ~~and~~ **or** insert the DPV vaginal matrix ring (25 mg) once every 4 weeks will experience similar distributions of pregnancy outcomes to the general population.

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 (29-35) 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”):

29. First sentence of last paragraph in Section 2.1, *Pregnancy and HIV in Sub-Saharan Africa*:

Two ~~such~~ ARV-based prevention interventions...

30. First sentence in Section 2.5.2, *Phase I and II Studies of DPV*:

Across all clinical trials conducted in healthy participants evaluating multiple VR ~~configurations~~ **formulations**, the DPV VR was generally ~~safe and~~ well-tolerated.¹²

31. First sentence of “Studies of the DPV VR in Pregnancy” sub-section in Section 2.5.3, *Phase III Studies of DPV*:

The use of DPV VR has been shown to be **well-tolerated** ~~safe and effective~~ for HIV-1 prevention in nonpregnant reproductive-aged women.

32. Third sentence of second paragraph and third sentence of “Ethical justification” sub-section in Section 2.9, *Rationale for Study Design*:

Although there have not been adequate and well-controlled trials of DPV VR and Truvada conducted in pregnant and/or postpartum women, to date, limited exposure data suggests these agents **could** ~~to be safe and effective~~ for women and their fetuses/infants.

MTN-042 affords the prospect of direct benefit to pregnant women and their infants in sub-Saharan Africa – a region where young women of reproductive age have high HIV acquisition rates² and limited access to HIV prevention options - with two products that have been shown to be ~~safe~~^{12,13,27,70} ~~and effective~~^{12,13,27,70} **in reducing well-tolerated and to reduce the said risk of HIV-1 infection** in non-pregnant populations^{12,13,27,70}.

33. First sentence of first paragraph in Section 10.1, *Overview and Summary of Design*:

The MTN-042 study is a multi-site, two-arm, randomized, open-label Phase 3b study evaluating the safety, adherence and acceptability profiles of two ~~safe and effective~~ HIV-1 prevention products...

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

Given that the DPV 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-042 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 DPV VR and PrEP and/or for the development of other ~~safe and effective~~ interventions to prevent HIV acquisition in pregnant women.

35. Second sentence of first bullet point in second bullet point list of Section 13.7.2, *Children*:

Both products being used in this study have been shown to be **well-tolerated and to provide a statistically significant reduction in the risk of HIV-1 infection for safe and effective in adults** ~~adult women~~ when used as instructed, but DPV is **still under consideration for potential regulatory approval as an HIV-1 prevention product** ~~has not been approved in the countries where the implementation of this study is planned,~~ and Truvada for oral PrEP has not yet been made widely accessible in **the countries where the implementation of this study is planned** ~~these countries.~~

The following revisions (36-42) were made to update information about DPV VR 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]) and IPM 032 (Dapivirine Ring Extended Access and Monitoring [DREAM]) studies:

36. First, fourth and fifth sentences in Section 2.5, *Clinical Studies – DPV*:

To date, a total of ~~29~~ **31** Phase 1 and Phase 2 clinical research studies of DPV have been conducted, ~~with all but two completed: eight~~ **ten** studies of DPV VRs (containing 25 mg, ~~298~~ **503** subjects received DPV VRs); ... two studies of DPV vaginal film (~~25-74~~ women received DPV vaginal film).

~~And, t~~ **Two Phase III 3B** open-label extension trials, IPM 032 (DREAM) and MTN-025 (HOPE), ~~are ongoing, and offering~~ the extended use of the DPV 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.**¹²

~~As of April 2018~~ **To date**, a total of ~~2989~~ **4100** adult women between 18 and 65 years of age have been exposed to the DPV VR across the clinical development program's **completed Phase 1-3B studies.**¹²

37. Second sentence in Section 2.5.2, *Phase I and II Studies of DPV*:

The Dapivirine Vaginal Ring-004 has been evaluated in ~~five~~ **eight** completed **Phase 1 and Phase 2** clinical research studies, each demonstrating the relative safety of this VR.¹²

38. First and last sentences of “MTN-025 (HOPE)” sub-section in Section 2.5.3, *Phase III Studies of DPV*:

MTN-025, the HIV Open-label Prevention Extension (HOPE) study, is **was** a multi-site, open-label, randomized, Phase 3b study ~~currently being~~ implemented in the ASPIRE clinical research sites.³²

~~At close of accrual, t~~ The HOPE study had 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, while 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 serious adverse events (SAE) 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 DPV 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.

39. “IPM 032 (DREAM)” sub-section in Section 2.5.3, *Phase III Studies of DPV*:

IPM 032, the Dapivirine Ring Extended Access and Monitoring (DREAM) study, is **was** a multi-site, open-label follow-on study to The Ring Study ~~currently being~~ implemented in six of the IPM 027 sites.³³ ~~Approximately 1700~~ **In total, 941** eligible HIV-uninfected former Ring Study participants, ~~as well as VR-naïve women aged 18-25, will~~ received the same **DPV** VR used in The Ring Study. Like the HOPE study, DREAM study participants ~~will be~~ **were** asked to use the **DPV** 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.

The ring was found to be well-tolerated in DREAM with a safety profile similar to The Ring Study. Most (95%) DREAM participants’ returned rings had residual DPV 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.

40. Last sentence of “Studies of the DPV VR in Pregnancy” sub-section in Section 2.5.3, *Phase III Studies of DPV*:

~~As of March 2018, 22 pregnancies were reported in the DREAM study and 53 on the HOPE study; while less than 50% of the pregnancy outcomes are available, no new~~ **No** safety signals were found and no congenital anomalies **or birth defects** were reported ~~in the available data.~~³² **observed in any of the 70 pregnancies that occurred among HOPE participants who may have used the ring early on in their pregnancy prior to discovery of the pregnancy and subsequent product use discontinuation.**³²

41. First sentence of the first paragraph, following the 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.**

There were no new safety concerns noted in the two DPV 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 DPV VRs have also been observed in women using placebo rings, and it is unclear if the observed mutations were transmitted or arose due to DPV 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** ~~selection of NNRTI resistance has not been observed in clinical research studies.~~

42. Last sentence of the first paragraph in the “Risks of the DPV VR” section of Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography)*, *MOTHER – COHORTS 1-4*:

~~Some women who used the ring in other studies have had: discharge from the vagina; pain, burning, or itchiness in the vagina; and~~ **urinary tract infections** ~~vaginal bleeding in between their usual periods.~~ **Less common side effects included: irritation, bruising, swelling, inflammation, wearing, and discharge from the cervix; bladder pain and inflammation; vaginal odor, itching, tearing, and discomfort; pelvic and abdominal pain and discomfort; and problems urinating.**

The following revision was made to correct the exclusion criterion for estimated creatinine clearance from “Grade 1 or higher” to “Grade 2 or higher”, given there is no Grade 1 creatinine clearance per the DAIDS AE Grading Table:

43. Exclusion criterion #6f in Section 5.3, *Exclusion Criteria*:

- f. Estimated creatinine clearance \geq Grade 4-2 (Cockcroft Gault formula).**

The remaining revisions (44-63) were made to correct additional inconsistencies, omissions and errors found in the protocol and consent form documents during the development of study implementation materials:

44. Section title and third sentence in Section 2.5.2, *Phase I and II Studies of DPV*:

~~Phase I and II~~ **1 and 3** Studies of DPV

MTN-029/IPM 039 was a Phase ~~I~~, open-label clinical study...

45. Section title and third sentence in the second paragraph of “MTN-020 (ASPIRE)” sub-section in Section 2.5.3, *Phase III Studies of DPV*:

~~Phase III~~ **3** Studies of DPV

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

46. Section title and first sentence of “Partners PrEP study” sub-section in Section 2.6.2, *Phase III Studies of FTC with TDF*:

~~Phase III~~ **3** Studies of FTC with TDF

The Partners PrEP study was a ~~phase III~~ **Phase 3** trial of TDF or Truvada...

47. First sentence in Section 2.7.2, *Truvada Tablet*:

Resistance in individuals seroconverting while taking Truvada has been assessed from 5 placebo-controlled, ~~Phase III~~ **3** studies.

48. Second sentence in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

~~Participants who have live births will have their infants enrolled into the study at the PPO Visit. If the PPO visit is missed, a subset of these procedures will be made up as part of an interim visit as outlined in the MTN-042 SSP Manual.~~

49. “Clinical” section of Table 9: PPO Visit – Infants in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

- Review/update delivery and antenatal care records
- **Review/update infant health records**

50. After the second sentence in Section 7.5.2, *1-week PPO Phone Contact*:

All participants will be asked about the outcome of their pregnancy, including the status of their infant at the time of delivery. ~~Participants who have live births will be~~

~~asked about their infants~~ **No infant procedures will occur during the phone contact unless the infant has already been enrolled.**

51. “Clinical” section of Table 13: 6-week PPO Visit – Infants in Section 7.5.3, *6-week PPO/Study Exit Visit (SEV)/Early SEV*:

- Review/update ~~delivery and postpartum care~~ **infant health** records

52. “Clinical” section of Table 14: Semi-annual PPO Visits in Section 7.6, *Semi-annual PPO Visits for Infants*:

- Review/update ~~delivery and antenatal/postpartum care~~ **infant health** records

53. Second sentence of the first paragraph in Section 7.7.3, *Participants Who Permanently Discontinue Study Product Use for Reasons other than Seroconversion or Loss of Pregnancy*:

Infants born to participants who are permanently discontinued from study product use will ~~also~~ continue follow-up visits with a ~~modified~~ **their original** study visit/procedure schedule until their originally scheduled study exit date.

54. Before the last bullet point in Section 7.7.5, *Interim Visits*:

- **To capture pregnancy outcome and/or infant health information (e.g., if a participant misses her PPO Visit).**

55. Third bullet point list in Section 7.11, *Clinical Evaluations and Procedures*:

- Vital signs
 - Temperature
 - Pulse
 - Blood pressure **(if indicated)**
 - Respirations
 - **Oxygen saturation (if indicated at sites with capacity)**
- ~~Gestational age estimation at birth~~

56. First and third sentences in the “Pelvic examination and specimen collection” subsection of Section 7.11, *Clinical Evaluations and Procedures*:

Pelvic examinations will be conducted per guidelines for naked eye inspection described in the WHO/CONRAD Manual for Standardization of Colposcopy for the Evaluation of Vaginal Products, Update 2004, available at ~~http://www.conrad.org/publications-13.html~~ **https://apps.who.int/iris/bitstream/handle/10665/69748/WHO_RHR_04.02_eng.pdf**.

Speculum exams will be **required at the Enrollment Visit; at all other visits they will be performed only as indicated** (e.g., abnormal discharge, pain) per the local standard of care.

57. After “Creatinine and calculation of creatinine clearance” bullet point in “Local Laboratory-Blood” sub-section of Section 7.12, *Laboratory Evaluations*:

- **Weight will be captured each time creatinine is measured in all participants in order to calculate creatinine clearance**

58. At the end of the “≥ Grade 2 creatinine clearance” bullet point list in Section 9.5, *Other Clinical Findings*:

NOTE: Absolute values for creatinine and creatinine clearance will be used to grade these AEs instead of changes from baseline due to absence of a true pre-pregnancy baseline measurement in this study population and due to normal fluctuations in these measurements during pregnancy.

59. Sixth sentence in Section 9.7, *Criteria for Early Termination of Study Participation*:

Participants will also be asked permission for study staff to contact them periodically up to one year after their pregnancy outcome to follow up on any potential pregnancy complications or mother and infant AEs that may occur after study exit **to obtain information about their pregnancy outcome and their infant’s health.**

60. “Clinical” section of table in Appendix II, *Table of Visits and Study Procedures – Infants*:

	PPO Visit	1-week PPO Phone Contact	6-week PPO Visit	6-month PPO Visit	12-month PPO Visit/ Early SEV
Review/update delivery and antenatal/postpartum care records	X		X	X	X
Review/update infant health records			X	X	X

61. Second bullet point in the “What procedures will be done for this study?” section of Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography)*, *MOTHER – COHORTS 1-4*:

We will ask your permission to access your medical records, **including your delivery records to gather information about your baby at the time of birth. We will also ask your permission** to contact your care provider, and to conduct a study visit as soon as possible after you have your baby.

62. After the last sentence of the second paragraph in the “Confidentiality” section of Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography)*, *MOTHER – COHORTS 1-4*:

[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 dapivirine vaginal ring is approved for use or the clinical research development program for the dapivirine vaginal ring is stopped.]

63. Second sentence in the “Risks of the DPV VR” sub-section of Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography)* – INFANT:

Babies of women who became pregnant while using the **DPV** ring in clinical studies did not **seem to** experience more side effects than babies of ~~non-pregnant~~ women **who used a ring without medication in it**, but there’s not enough information to know for sure.

64. Last sentence of the second paragraph in the “Confidentiality” section of Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography)* – INFANT:

All original study documents that provide information about your baby for this study will be kept for at least two years after either the **dapivirine** vaginal ring is approved for use or **the clinical research development program for** ~~on~~ the **dapivirine** vaginal ring is stopped.

65. Protocol references to the DPV VR IB were updated to the most current version dated 11 November 2019.

66. Protocol Team Roster – Deletions: Jennifer Thomas and Nicole Macagna.

67. Protocol Signature Page was updated to include Letter of Amendment #1; 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-042

Phase 3b, Randomized, Open Label Safety Trial of Dapivirine Vaginal Ring and Oral TRUVADA® Use in Pregnancy

INVESTIGATOR SIGNATURE FORM

Version 1.0; April 16, 2019

Letter of Amendment #01; December 17, 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: 38544)

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