

LETTER OF AMENDMENT #01 TO:

MTN-043

Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

Version 1.0, dated July 24, 2019

**DAIDS Protocol #38591
IND #139598**

Date of Letter of Amendment: 16 April 2020

Site Instruction

The following information impacts the MTN-043 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-043. The purpose of this LoA is to clarify an exclusion criterion, HIV testing procedures for infant whose mother seroconverts on study, grading criteria for infant AE related to fever, and reporting criteria for HIV acquisition. It also updates information about DPV VR studies, updates information about the risks of DPV VR to be consistent with the recently updated IB, adds explicit mention of mental health assessments to the protocol and consent forms, adds language about consent for off-site visits for baby, makes other minor edits to correct additional inconsistencies, omissions and errors in the protocol and consent forms, and update reference to the updated DPV VR IB.

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 #6c in Section 5.3.1, *Exclusion Criteria - Mother*, to correct the 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

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

The following revisions (2-3) were made to clarify that HIV acquisition will not be reported as AEs and to add the AE grading criteria for infant AEs related to fever:

2. At the end of the bullet list of the fifth paragraph 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, and PSRT.**
3. After the set of bullet points of the fifth paragraph in Section 8.3.1, *Adverse Events*:

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

- **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: \geq 102.9°F (\geq 39.4°C)**
4. The following revisions were made to the first and fourth paragraph in Section 7.5.1, *Participants Who Become Infected with HIV*, to clarify the follow-up procedures for an infant whose mother seroconverts on study:

If a mother seroconverts on study, her infant **will be tested immediately and if negative, will need to have an additional PCR testing visit 12 weeks after seroconversion is diagnosed, as described** stated below. **Counselling on interim infant feeding method will also be provided per local care standard.** Protocol-specified procedures for the monthly study visits for the mother or the infant will continue except the following:

Upon confirmation of maternal HIV infection, the following procedures are performed on the infant at the following timepoints:

- **Infant HIV testing by ~~Either HIV-1 RNA PCR, or DNA PCR, (or other local Standard of Care testing)~~** will be performed at the clinic visit immediately following confirmation of the maternal HIV infection ~~and 12 weeks later.~~
- **If the infant is HIV negative at the time of maternal seroconversion, infant HIV testing (as described above) will be repeated at 4-6 weeks later.**
- **If infant testing continues to be negative at the 4-6 weeks test, it should be repeated again at 12 weeks after confirmation of the maternal infection.**
- Upon confirmation of infant HIV infection:
 - Repeat HIV-1 RNA PCR test and do 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 LC.
 - Facilitate rapid referral of the infant for appropriate further management including necessary blood tests (CD4+ T cell count, FBC), urgent ART

initiation, and adherence counselling and follow -up for the mother/guardian

The following additions (5-8) were made to add review of available postpartum care records for mothers at Screening and Enrollment visits in Section 7, Study Procedures, Appendix I and Appendix V:

5. After the bullet point of “Review medical history” or “Review/update medical history” in Table 3: Visit 1 – Screening Visit - Mothers, of Section 7, Study Procedures:

| | |
|-----------------|--|
| Clinical | <ul style="list-style-type: none"> Review medical history Review available postpartum care records Infant feeding assessment |
|-----------------|--|

6. After the bullet point of “Review medical history” or “Review/update medical history” in Table 5: Visit 2 – Enrollment Visit - Mothers, of Section 7, Study Procedures:

| | |
|-----------------|---|
| Clinical | <ul style="list-style-type: none"> Review/update medical history Review available postpartum care records* Infant feeding assessment |
|-----------------|---|

7. In “Clinical” category in Appendix I, Table of Visits and Study Procedures – Mothers:

| | Visit 1 SCR | Visit 2 ENR | Visits 3,4 (Week 1, 2) | Visits 5, 6 (Month 1, 2) | Visit 7 (Month 3 PUEV) | Visit 8 SEV (2 weeks after PUEV) | Early Termination Visit |
|---|----------------|----------------|---------------------------|-----------------------------|------------------------------|--|-------------------------------|
| CLINICAL | | | | | | | |
| Review/update medical history | X | X | X | X | X | X | X |
| Review available postpartum care records | X | * | | | | | |

8. Second bullet point of the third paragraph in the “Study Procedures:” sub-section in Appendix V: Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit) – Mother & Infant:

- We will ask your permission to access your study medical records and **your available postpartum care records.**

The following revisions (9-10) were made to include explicit mention of mental health assessments for participants in this study’s protocol and consent form documents:

9. After the last sentence in Section 7.9, Counseling:

Participants will be monitored for symptoms of depression throughout their participation in the study. A validated depression scale designed for use with postpartum women will be administered.⁶⁸ Participants will be referred to additional counseling and/or mental health services if clinically indicated.

10. After the first sentence of the first bullet point in the “Study Procedures” section of Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit), Mother & Infant*:

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

The following revisions (11-12) were made to clarify the general criteria for permanent discontinuation of study product for participants who become pregnant, and to clarify product use consideration for observed deep epithelial disruption in participants randomized to the ring:

11. At the last bullet point of the first paragraph in Section 9.3, *General Criteria for Temporary/Permanent Discontinuation of Study Product*:

Participants will be permanently discontinued from study product by the IoR/designee for any of the following reasons:

....

- Reported use of PrEP for HIV prevention outside of the study.
- Reported use of PEP for potential HIV exposure.
- Non-therapeutic injection drug use.
- Pregnancy (**See Section 7.5.2**).

12. Second sentence of the second paragraph in Section 9.4, *Temporary Product Hold/Permanent Discontinuation in Response to Observed Adverse Events*:

The following outlines product use considerations for observed adverse events. Except for deep epithelial disruption **observed in participants randomized to use the DPV VR**, study product use will depend on the adverse event grade and relationship to study product.

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. The following revisions (13-15) were made to replace all protocol descriptions of the DPV VR as “safe” and “effective” with more precise terms (e.g., “well-tolerated”, “significantly reduces risk of HIV-1 infection”):

13. First sentence in Section 2.7.2, *Phase 1 and 2 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**.

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

DPV VR as tested in MTN-020 (ASPIRE), **MTN-025 (HOPE)**, and IPM 027 (The Ring Study) **and IPM 032 (DREAM)** was well-tolerated and showed a ~30% risk reduction in the risk of HIV-1 infection in the Phase 3 trials (MTN-020 and IPM 027). ~~and DPV VR~~ is being considered for potential regulatory approval. Furthermore, Truvada is an FDA and EMA approved product that is used to treat HIV infection as well as reduce the risk of HIV-1 infection.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may help to understand issues important for broader implementation of the DPV VR and **Truvada for oral PrEP** and/or for the development of other ~~safe and effective~~ interventions to prevent HIV acquisition in breastfeeding women.

15. Second sentence of first bullet point in Section 13.7.2, *Children*:

The 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 adult women** ~~safe and effective in adults~~ when used as instructed, but the DPV VR **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 the study is planned** ~~these countries~~.

The following revisions (16-23) were made to update information about DPV VR clinical trials 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:

16. Fourth, seventh and eighth sentences in Section 2.7, *Clinical Studies – DPV*:

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

Two Phase 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 who were assigned to the placebo rings in the Phase 3 trials.**¹²

~~As of April 2018~~ **To date**, a total of ~~3422~~ **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

17. Second sentence in Section 2.7.2, *Phase 1 and 2 Studies of DPV*:

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

18. “MTN-025 (HOPE)” sub-section in Section 2.7.3, *Phase 3 Studies of DPV*:

~~At close of accrual,~~ 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 DPV-related drug resistance was found among the 35 HOPE participants who acquired an HIV infection during the study.²⁷

19. “IPM 032 (DREAM)” sub-section in Section 2.7.3, *Phase 3 Studies of DPV*:

~~Enrollment was completed in February 2018. In total, 941 eligible HIV-uninfected former Ring Study participants received the same DPV VR used in The Ring Study. Like the HOPE study (described below), the DREAM study participants were asked to use the DPV VR for up to at least 12 months, replacing it monthly, and to attend monthly visits for the first one to three months of the study with follow-up visits quarterly thereafter. At the close of accrual, the DREAM study had enrolled a total of 941 former IPM-027 participants who were HIV-negative and otherwise eligible to enroll.~~

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.

20. Last sentence of the first paragraph in the “Studies of the DPV VR in Pregnancy” sub-section in Section 2.7.3, *Phase 3 Studies of DPV*:

~~As of March 2018, 22 pregnancies were reported in the DREAM study and 53 in the HOPE study; while less than 50% of the pregnancy outcomes are available, no new safety signals have been found and no congenital anomalies were reported in the~~

~~available data.~~²⁷ **No safety signals were found and no congenital anomalies or birth defects were 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.**²⁷

21. 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 **has been associated with** ~~may lead to discharge from the vagina; pain, burning, or itchiness in the vagina; vaginal bleeding in between usual periods; and urinary tract infections,~~ **vaginal discharge, vulvovaginal pruritus, vulvovaginitis, and pelvic pain.** Less commonly reported conditions ~~side-effects include: pelvic inflammatory disease, cervix erythema, cervix edema, cervicitis, urinary incontinence, dyspareunia, headache, decreased neutrophil count, abnormal weight loss, and dysmenorrhea.~~ **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.~~

22. Seventh bullet points in the “Study Summary” sub-section of Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit) – Mother and Infant*:

- Some common risks or discomforts from the ring include: vaginal irritation, discharge, and/or discomfort, **pelvic pain** and **urinary tract infections.** ~~allergic reaction.~~ One serious but rare **potential risk** ~~side-effect~~ is toxic shock syndrome caused by poisons (toxins) released by some types of *Staphylococcus aureus*, a common bacterium. So far, this has not been reported in users of the DPV VR, however it has been reported in users of other vaginal rings on rare occasions.

23. After the first sentence of the first paragraph in the “Risks of the DPV Ring” section of Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit) – Mother and Infant*:

We do not yet know all the side-effects of the ring. Some women who used the ring in other studies have had discharge from the vagina; pain, burning, or itchiness in the vagina; ~~vaginal bleeding in between their usual periods~~ **pelvic pain** and urinary tract

infections. Less commonly **reported conditions** ~~side effects~~ include **irritation, bruising, swelling, inflammation, and discharge from the cervix; bladder pain and inflammation; vaginal odor and discomfort; pelvic and abdominal pain and discomfort; and problems urinating.** ~~pelvic inflammatory disease, cervix erythema, cervix edema, cervicitis, urinary incontinence, dyspareunia (difficult or painful sexual intercourse), headache, decreased neutrophil count, abnormal weight loss, and dysmenorrhea (pain and cramping during periods).~~

The remaining revisions (24-35) were made to correct additional inconsistencies, omissions and errors found in the protocol and consent form documents during the development of study implementation materials:

24. Third sentence of the second paragraph in the “MTN-020 (ASPIRE)” sub-section in Section 2.7.3, *Phase 3 Studies of DPV*:

In pre-defined as-randomized subgroup analyses, HIV-1 protection differed significantly by age, with a 61% reduced risk of HIV-1 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).

25. In Table 3 in Section 7.2, *Visit 1: Screening Visit*, and *Appendix I: Table of Visits and Study Procedures – Mothers*:

| Visit 1 – Screening Visit - Mothers | |
|-------------------------------------|---|
| Component | Procedures |
| Administrative and Regulatory | <ul style="list-style-type: none"> Obtain informed consent for screening and enrollment[^] Obtain signed medical records release (if required per local laws/regulations) and pediatric care provider information |

| | Visit 1 SCR | Visit 2 ENR | Visits 3,4 (Week 1, 2) | Visits 5, 6 (Month 1, 2) | Visit 7 (Month 3 PUEV) | Visit 8 SEV (2 weeks after PUEV) | Early Terminati on Visit |
|---|----------------|----------------|---------------------------------|-----------------------------------|---------------------------------|--|--------------------------------|
| ADMINISTRATIVE AND REGULATORY | | | | | | | |
| Obtain signed medical records release (if required per local laws/regulations) and pediatric care provider information | X | | | | | | |

26. Fourth bullet point in Study Product/Supplies of Table 9 in Section 7.4.2, *Visit 5 and 6 (1-month and 2-month Visits)*, and in *Appendix I: Table of Visits and Study Procedures – Mothers*:

| | |
|------------------------|---|
| Study Product/Supplies | <ul style="list-style-type: none"> Remove and/or collect study VR or unused study tablets Provide study VR or study tablets Provide product use instructions Insertion/removal of study VR at the clinic (clinician to check VR placement, as needed) or DOD of first study tablet Offer male condoms |
|------------------------|---|

| | Visit 1 SCR | Visit 2 ENR | Visits 3,4 (Week 1, 2) | Visits 5, 6 (Month 1, 2) | Visit 7 (Month 3 PUEV) | Visit 8 SEV (2 weeks after PUEV) | Early Terminati on Visit |
|---|----------------|----------------|---------------------------------|-----------------------------------|---------------------------------|--|--------------------------------|
| STUDY PRODUCT | | | | | | | |
| Insertion/removal of study VR at the clinic (clinician to check VR placement) or DOD of first study tablets | | X | | X | | | |
| Check VR placement | | X | | * | | | |

27. Second bullet point in Behavioral/Counseling of Table 13 in Section 7.4.4, *Visit 8 – Study Exit Visit (SEV) – Two weeks after PUEV*, and Appendix I. An asterisk was added to make HIV pre-/post-test counselling as indicated at Visit 8.

| Visit 8 – SEV (2 weeks after PUEV) - Mothers | |
|--|---|
| Component | Procedures |
| Behavioral/Counseling | <ul style="list-style-type: none"> Social harms assessment HIV pre- and post-test counseling* HIV/STI risk reduction counseling* Contraception counseling PrEP counselling |

| | Visit 1 SCR | Visit 2 ENR | Visits 3,4 (Week 1, 2) | Visits 5, 6 (Mont h 1, 2) | Visit 7 (Month 3 PUEV) | Visit 8 SEV (2 weeks after PUEV) | Early Terminati on Visit |
|--------------------------------|----------------|----------------|---------------------------------|------------------------------------|---------------------------------|--|--------------------------------|
| BEHAVIORAL | | | | | | | |
| HIV Pre-/Post-test counselling | X | X | * | X | X | * | X |

28. Second sentence of the first paragraph in Section 7.4.4, *Visit 8 – Study Exit Visit (SEV)*:

The Visit 8, Study Exit Visit (SEV) will occur two weeks (i.e., approximately 14 days) after the PUEV. This visit can occur no earlier than 7 days before the target date and no later than 14 days after the **PUEV target date**.

29. At the beginning of the bullet list of the second paragraph in Section 7.5.2, *Participants Who Become Pregnant*:

Upon documentation of the pregnancy, the following procedures must be performed regardless of whether they are scheduled to be completed:

- **Creatinine**
- CBC with platelets
- AST/ALT
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments

30. Third bullet point of the first bullet point list in Section 7.12 for physical exams of the mothers, *Clinical Evaluations and Procedures*:

- General appearance
- ~~Height~~
- Weight
- Abdomen*
- Head, eye, ear, nose and throat (HEENT)*
- Height*

31. First bullet point and last bullet point of the second bullet point list in Section 7.12 for physical exams of infants, *Clinical Evaluations and Procedures*:

- Vital signs
 - Temperature
 - Pulse
 - Blood pressure (**if indicated**)
 - Respirations
- General appearance
- ...
- Ages and Stages® assessment (**at Enrollment and PUEV exams only**)
**May be omitted after the Screening Visit.*

32. Last sentence in Section 10.8.4, *Missing Data*:

For a univariate binary and quantitative outcome, respectively, a generalized linear model with a binomial or Normal error distribution will be used for estimation and testing. ~~Sensitivity analyses will be conducted comparing the regimens using only the first study product use period data for all the outcomes.~~

33. At the beginning of the third paragraph in the “Study Products” sub-section of Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit) – Mother and Infant*:

Both the DPV VR and Truvada contain anti-HIV medication and reduce the risk of HIV-1 infection. Neither product can guarantee protection from HIV. Neither study product is effective against common sexually transmitted diseases other than HIV.

34. Second sentence of the fourth paragraph in the “Risks of the DPV Ring” section of Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, and Off-Site Visit) – Mother and Infant*:

Women who became pregnant while using the ring in clinical studies did not **seem to** experience more side-effects than ~~non-pregnant~~ women **who used a ring without medication in it**, and neither did their babies. However, there is not enough information to know for sure. There is currently no reason to suspect that using the ring will change the amount or taste of milk for babies.

35. Third sentence of the first paragraph, third sentence of the second paragraph, and the signature form of the Consent for Off-Site Visits in Appendix V:

For example, if you need to receive a new ring or to have a urine or blood sample collected, **or if your baby needs a blood sample collected**, study staff could come to ~~you~~ your home or meet you at another location, if you give your permission and if the study staff determine that it is appropriate.

Choosing not to have study visit procedures outside of the study clinic will not affect your **or your baby’s** participation in this study. Even if you agree today, you can withdraw your consent for off-site visits **for you and your baby** at any time by providing your request in writing to the person in charge of this study.

| PARTICIPANT INITIALS OR MARK | | |
|------------------------------|-------|--|
| _____ | _____ | I DO agree to have study visit procedures for me and my baby at a location other than the study clinic by clinic staff, when necessary. |
| Initials or Mark | Date | |
| _____ | _____ | I DO NOT agree to have study visit procedures for me and my baby at a location other than the study clinic by clinic staff, when necessary. |
| Initials or Mark | Date | |

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

37. Two references were added to support the revised content as specialized in item 9 and item 19 of this LoA.

- **Cox, J.L., Holden, J.M., & Sagovsky, R. 1987. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry* 150:782-786.**
- **Baeten J, Palanee-Phillips T, Mgodini N, Ramjee G, Gati B, Mhlanga F, Hunidzarira P, Mansoor LE, Siva S, Govender V, Manganani B, Naidoo L, Singh N, Nair G, Chinula L, Mayo AJ, Szydlo D, Soto-Torres L, Nel A, Rosenberg Z, Hillier S, Brown E, MTN-025/HOPE Study Team. High adherence and sustained impact on HIV-1 incidence: final results of an open-label trial of the dapivirine ring. *International AIDS Society - Conference on HIV Science, 21 - 24 July 2019, MEXICO CITY, MEXICO; Abstract #TUAC0203.***

38. 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-043

Phase 3B, Randomized, Open-Label, Safety, and Drug Detection Study of Dapivirine Vaginal Ring and Oral TRUVADA® in Breastfeeding Mother-Infant Pairs

INVESTIGATOR SIGNATURE FORM

Version 1.0; July 24, 2019

Letter of Amendment #01; April 16, 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: 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