

LETTER OF AMENDMENT #02 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: 9 June 2020

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 add consent language emphasizing that neither study product guarantees protection from HIV as recommended by several site IRBs/ECs. This LoA also adds behavioral assessments after participants' pregnancy outcome for all Cohorts as well as a baseline behavioral assessment for Cohort 1, allows retrospective HIV RNA testing on enrolled participants who acquire an HIV infection, allows retrospective testing related to COVID-19 infection on enrolled participants if such testing becomes available in the future, clarifies requirements related to participants' release of medical records, and adds IMPAACT 2009 study results. This LoA also includes information related to COVID-19's impact on study implementation: the content of the planned behavioral assessments may include questions related to the impact of the COVID-19 pandemic on the context of participants' HIV prevention and study product use; the overall study duration at study sites may be affected by COVID-19 closures; and changes to procedures may be implemented to mitigate potential hazards to participants or due to public health emergencies at the study sites. Lastly, this LoA makes other minor edits to correct additional inconsistencies, omissions and errors in the protocol, and updates RTI International's address and the Protocol Team roster.

Unless otherwise noted below, text to be deleted is noted by ~~strikethrough~~, text to be added is noted in **bold**, and text in ***bold italics*** is not to be added, but to serve as a clarification of the implementation item in question.

Detailed Listing of Revisions

The following revisions (1-4) were made to add consent language emphasizing that neither study product guarantees protection from HIV, as recommended by several site IRBs/ECs:

1. First sentence of eighth bullet point of “Study Summary” section in Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 1-4*:

You will be using a study product that may prevent you from getting HIV if you use it consistently, **but neither study product can guarantee protection from HIV.**

2. After the last sentence of “Study Details – Study Products” section in Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 1-4* and in Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), INFANT*:

Neither study product can guarantee protection from HIV.

3. First sentence of “Benefits” section in Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 1-4*:

You will be using one of two study products that may prevent you from getting HIV if you use it consistently, **but neither study product can guarantee protection from HIV.**

4. First sentence of “Benefits” section in Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography), INFANT*:

You will be using one of two study products that may prevent you, and therefore your baby, from getting HIV if you use it consistently, **but neither study product can guarantee protection from HIV.**

The following revisions (5-11) were made to add behavioral assessments after participants’ pregnancy outcome for all Cohorts as well as a baseline behavioral assessment for Cohort 1:

5. “Behavioral/Counseling” section of Table 3: Visit 2 – Enrollment Visit in Section 7.3, *Visit 2: Enrollment Visit (Day 0)*:

- Baseline behavioral assessment (~~Cohorts 2-4 only~~)

6. “Behavioral/Counseling” section of Table 8: PPO Visit – Mothers in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

- **Behavioral assessment (Cohorts 2-4 only)**

7. “Behavioral/Counseling” section of Table 12: 6-week PPO/SEV/Early SEV – Mothers in Section 7.5.3, *6-week PPO/Study Exit Visit (SEV)/Early SEV*:

- **Behavioral assessment**

8. Second and third sentences of the first paragraph in Section 7.9, *Behavioral Evaluations*:

A Baseline Behavioral Questionnaire will be administered in the clinic at the Enrollment Visit to all participants in Cohorts ~~2-4~~ **1-4**. **All participants will be asked about the context of HIV prevention and study product use, while participants in Cohorts 2-4** will be asked **more** detailed questions about sexual behavior, HIV prevention method use and intravaginal practice history, and about their attitudes towards the attributes of the study product, their attitudes and perceptions about using the study product during pregnancy, and other preliminary acceptability measures of the study product.

9. At the end of the first paragraph in Section 7.9, *Behavioral Evaluations*:

Participants in Cohorts 2-4 will complete a brief Post-PPO Behavioral Questionnaire at their PPO Visit and all participants will complete a Behavioral Questionnaire at their SEV, which may include follow-up questions about the context of study product use.

10. “Behavioral” 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)				
Behavioral assessment (Cohorts 2-4 only)		X			φ		X (Cohorts 2-4 only)		X

11. Bullet point added to “What procedures will be done for this study?” section in Appendix V, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORT 1*:

- **At some visits, you will answer questions about using the study products and other behaviors, including sexual activity. Some of the questions may be sensitive. If you ever feel uncomfortable, you can choose not to answer questions at any time. Your answers will be kept confidential and no one other than the study team will have access to your responses.**

The following revisions (12-13) were made to allow retrospective HIV RNA testing on enrolled participants who acquire an HIV infection to better understand the timing of infection:

12. Last bullet point of third paragraph in Section 7.7.1, *Participants Who Become Infected with HIV*:

- HIV-1 genotyping will be performed on the stored plasma closest to the time of ~~confirmed~~ HIV-1 infection.

- **HIV-1 RNA PCR or HIV-1 genotyping** It may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).

13. Last bullet point of fifth paragraph in Section 7.7.1, *Participants Who Become Infected with HIV*:

- At all subsequent scheduled clinic visits until the infant is one year old, perform plasma collection, CD4+ T cell count and HIV-1 RNA PCR. **HIV-1 RNA PCR or 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).

The following revisions (14-16) were made to allow retrospective testing related to COVID-19 infection on enrolled participants if such testing becomes available in the future, to better understand the pandemic’s potential contribution to study safety endpoints:

14. Added bullet point to “Laboratory Center – Blood” sub-section in Section 7.12, *Laboratory Evaluations*:

- **COVID-19 infection testing**
 - **Testing related to COVID-19 infection would only be performed retrospectively on stored plasma samples if such testing is available and deemed necessary to better understand the impact of COVID-19 infection on the study safety endpoints.**

15. Second sentence of first paragraph in “Consent for Storage and Future Testing of Specimens and Related Health Information” section of Appendices V-VIII, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage and Off-Site Visit), MOTHER – COHORTS 1-4*:

We would like to store your leftover body fluids for future work that could include testing for study products, and testing for HIV risk **and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data).**

16. Second sentence of first paragraph in “Consent for Storage and Future Testing of Specimens and Related Health Information” section of Appendix IX, *Sample Informed Consent Form (Screening, Enrollment, Long-Term Storage, Off-Site Visit, and Photography) INFANTS*:

We would like to store your baby’s leftover body fluids for future work that could include testing for study products, and testing for HIV risk **and testing related to COVID-19 infection (if such testing is available and needed to better understand the impact of COVID-19 infection on the study data).**

The following revisions (17-20) were made to clarify requirements related to participants’ release of medical records, to specify that signed medical records release is required only if sites’ IRBs/ECs require it:

17. Fourth sentence of Section 7.2, *Visit 1: Screening Visit*:

Participants will also provide ~~written~~ permission for the study site to obtain copies of their antenatal records, including laboratory and ultrasound results, for review prior to final confirmation of eligibility. **If required per local laws and regulations, signed record release forms will be obtained.**

18. “Administrative and Regulatory” section of Table 2: Visit 1: Screening Visit in Section 7.2, *Visit 1: Screening Visit*:

- Obtain signed medical records release and antenatal care provider information **(if required per local laws/regulations)**

19. “Administrative and Regulatory” section of Table 8: PPO Visit 1 – Mothers in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

- Review/update signed medical records release and delivery care provider information **(if required per local laws/regulations)**

20. “Administrative and Regulatory” 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)				
Obtain/review/update signed medical records release and antenatal/delivery care provider information (if required per local laws/regulations)	X						X		

The following revisions (21-22) were made to update the IMPAACT 2009 study description and add study results:

21. After the second sentence of “IMPAACT 2009” sub-section in Section 2.6.2, *Phase 3 Studies of FTC with TDF*:

Prior to initiation of the main study component, a PK study component was implemented to establish adherence benchmarks for tenofovir diphosphate (TFV-DP) in dried blood spots (DBS) for pregnant (14-24 weeks gestation at Enrollment) and postpartum (6-12 weeks postpartum at Enrollment) adolescents and young women who took PrEP daily under direct observation, and to compare these benchmarks in the pregnant and postpartum groups. Twenty pregnant and twenty postpartum women enrolled in the PK study component and took PrEP daily for twelve weeks, with >99% of oral PrEP doses taken under direct observation. Consistent with other studies, TFV-DP in DBS was 31-37% lower in pregnant women compared with postpartum women. As of Q3-2018-Q2 2020, the main study component is paused open to accrual in Zimbabwe, Malawi, Uganda, and South Africa

pending further analysis of PK study component results.⁴⁵ No **safety** data will be available from this study prior to initiation of MTN-042.

22. Fourth sentence of “Community support” sub-section in Section 2.9, *Rationale for Study Design*:

And though IMPAACT 2009 (**which** ~~only~~ recently **completed its initial PK component open to accrual**) will be evaluating the safety of PrEP in adolescent and young women during pregnancy, stakeholders felt that, together, both studies would contribute much needed data about the safety of PrEP in pregnant women.

23. The following clarification applies to the first sentence of the first paragraph and the second sentence of the second paragraph of Section 7.9, *Behavioral Evaluations*, and was added at the end of that section:

Behavioral endpoints will be assessed via CRFs.*

All IDIs will be conducted by trained and experienced facilitators to gain further insight on the social and behavioral issues described above.*

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

24. The following clarification applies to the first sentence of Section 4.4., *Time to Complete Accrual*; and to the second and sixth sentences of Section 10.5, *Participant Accrual, Follow-up and Retention*; and was added at the end of both sections:

Time to complete accrual will be approximately 4 to 9 months for recruitment and enrollment of each Cohort, with accrual pauses of approximately 3 to 8 months between Cohorts to allow all enrolled participants to give birth and for interim safety analyses to be conducted before continuing to the next Cohort, for a study duration of approximately 38-50 months.*

The accrual period for Cohorts 1-3 will be approximately 4-5 months, while the accrual period for Cohort 4 will be approximately 7-9 months; Cohort 4 was designed to be larger in order to accumulate more person-years of observation and to better evaluate less frequent outcomes, such as pregnancy loss in the second trimester, after comprehensive evaluation of safety in the preceding Cohorts.*

Therefore, it is expected that the Cohort 1 phase of the study will last approximately 7-9 months, Cohort 2 approximately 8-11 months, Cohort 3 approximately 10-13 months, and Cohort 4 approximately 13-17 months, for a study duration of approximately 38-50 months.*

*** Overall study duration – from first enrollment through closure of all follow-up – may be longer than planned if temporary site closures due to the COVID-19 pandemic cause delays or pauses in enrolling participants at one or more research sites.**

25. The following clarification applies to the first sentence of Section 13.1, *Institutional Review Boards/Ethics Committees*, and was added at the end of that section:

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

*** Changes to this protocol may be implemented by investigators prior to IRB/IEC approval, if those changes are required to eliminate apparent immediate hazards to the study participant. [See 45 CFR 46.108(a)(3)(iii) under the 2018 Requirements and 45 CFR 46.103(b)(4)(iii) under the pre-2018 Requirements.] These changes must be documented as Protocol Deviations and reported to the Protocol Team and IRB/IEC as soon as possible. [See ICH E6(R2), Good Clinical Practice, Section 4.5.4.] In the event of a public health emergency, investigators should adhere to the recommendations of their local institutions, IRB/IEC and local health departments. When conflicts exist between local directives, MTN, Protocol Team and/or DAIDS policies or guidance, sites should follow the requirement that is most protective of study participants and site staff. [See DAIDS Guidance, Coronavirus Disease (COVID-19) and DAIDS HIV/AIDS Network Clinical Research Studies, Page 3, dated March 13, 2020.]**

The remaining revisions (26-38) were made to correct additional inconsistencies, omissions and errors in the protocol document:

26. “Clinical” section of Table 3: Visit 2 – Enrollment Visit in Section 7.2, *Visit 2: Enrollment Visit (Day 0)*, Table 5: Bi-weekly Visits After 36th Week of Gestation in Section 7.4.2, *Bi-weekly Visits After 36th Week of Gestation*, and Table 7: 4-week Visit(s) (Cohorts 2-4) in Section 7.4.4, *4-week Visit(s) (Cohorts 2-4)*:

- Review/update **available** ultrasound results and antenatal care records

27. “Clinical” section of Table 8: PPO Visit – Mothers in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

- Review/update **available** delivery and antenatal care records

28. “Clinical” section of Table 12: 6-week PPO/SEV/Early SEV – Mothers in Section 7.5.3, *6-week PPO/Study Exit Visit (SEV)/Early SEV*:

- Review/update **available** delivery and postpartum care records

29. “Study Products/Supplies” 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*:

- Insertion of study VR at the clinic (clinician to check VR placement, as needed) (for DPV group)* **or DOD of first study tablet (for Truvada group) [^]**

[^] Required if product resupply occurs during visit

30. “Study Products/Supplies” section of Table 7: 4-week Visit(s) (Cohorts 2-4) in Section 7.4.4, *4-week Visit(s) (Cohorts 2-4)*:

- Insertion of study VR at the clinic (clinician to check VR placement, as needed) (for DPV group)* **or DOD of first study tablet (for Truvada group)**

31. “Study Products/Supplies” section of Table 8: PPO Visit – Mothers in Section 7.5.1, *Post-Pregnancy Outcome (PPO) Visit*:

- Remove and/or collect study VR or study tablets **(if final VR or tablets not already collected)**

32. Fourth sentence in Section 7.4.1, *Phone Contacts Prior to Pregnancy Outcome*:

~~For all participants~~ **Beginning on their 36th week of gestation until pregnancy outcome**, this phone contact (or visit, if needed) will **also** occur every odd-numbered week following their ~~36th week of gestation until pregnancy outcome~~ **of study participation.**

33. Second sentence in Section 7.4.2, *Bi-weekly Visits After 36th Week of Gestation*:

This means that participants in Cohort 1 will have bi-weekly follow-up visits every two weeks (i.e., approximately 14 days) following their Enrollment Visit until pregnancy outcome. **Beginning on their 36th week of gestation until pregnancy outcome**, and participants in Cohorts 2-4 will have bi-weekly follow-up visits every even-numbered week following their ~~36th week (inclusive)~~ of gestation until pregnancy outcome **of study participation.**

34. Second sentence in Section 7.4.4, *4-week Visit(s) (Cohorts 2-4)*:

For Cohorts 3 and 4, this visit will also occur every 4 weeks after their first 4-week Visit until their 36th week (inclusive – this visit ~~can~~ **should** occur in the 36th week) of gestation.

35. Section 9.5, *Other Clinical Findings*, last bullet point of “≥ Grade 2 creatinine clearance” sub-section:

- ~~If either retesting cannot occur within one week or if retesting yields a result of ≥ Grade 1~~, the IoR/designee must consult the PSRT for further guidance on resuming product use.

36. Section 9.5, *Other Clinical Findings*, last bullet point of “≥ Grade 2 glycosuria or proteinuria” sub-section:

- If either retesting cannot occur within one week or if retesting yields a result of ~~≥~~ Grade 1, the IoR/designee must consult the PSRT for further guidance on resuming product use.

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

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

			Outcome	Visit		36 th Week			SEV/ Early SEV
In-depth interview (subset)					♦	♦ (subset)			

38. “Study Products/Supplies” 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)				
Insertion of study VR at the clinic (clinician check of VR placement done with initial insertion by participant; check done as needed for subsequent VRs) or DOD of first study tablet		X			X	* ^v			
Remove and/or collect study VR or study tablets					X	*	X (if final VR or tablets not already collected)		

^v Required if product resupply occurs during visit

39. Replaced citation #45 in the References section with an updated reference for the IMPAACT 2009 study description cited in second to last sentence of “IMPAACT 2009” subsection of Section 2.6.2, *Phase 3 Studies of FTC with TDF*:

45. ~~IMPAACT 2009 (DAIDS ID 30020): Feasibility, Acceptability and Safety of Oral Pre-Exposure Prophylaxis for Primary HIV Prevention During Pregnancy and Breast Feeding in Adolescents and Young Women. 2016. (Accessed 9/1/2016, 2016, at <http://impaactnetwork.org/studies/IMPAACT2009.asp>.) Anderson PL, Stranix-Chibanda L, Huang S, Hosek S, Kacanek D, Nematadzira T, Taulo F, Korutaro V, Nakabiito C, Masenya M, Lypen K, Chakhtoura N, Spiegel HM, Chi BH, on behalf of the IMPAACT 2009 team. TFV-DP in DBS for pregnant/postpartum adolescent and young women on PrEP in Africa. Poster #0980 presented at 2020 Conference on Retroviruses and Opportunistic Infection (CROI), March 8-11, 2020.~~

40. Section 1.5, *Data Centers*:

Women’s Global Health Imperative Program
RTI International

~~351 California Street, Suite 500
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41. Protocol Team Roster – Deletions: Karen Patterson, Felix Mhlanga.

42. Protocol Team Roster – Updates:

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43. Protocol Team Roster – Additions:

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44. Protocol Signature Page was updated to include Letter of Amendment #2; it is appended to the end of this document.

The above information, in addition to the changes from Letter of Amendment #1, 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

Letter of Amendment #02; June 9, 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