LETTER OF AMENDMENT #01 TO:

MTN-034/IPM 045

A Phase 2a Crossover Trial Evaluating the Safety of and Adherence to a Vaginal Matrix Ring Containing Dapivirine and Oral Emtricitabine/Tenofovir Disoproxil Fumarate in an Adolescent and Young Adult Female Population

Version 1.0, dated 2 February 2017

DAIDS Protocol #12066
IND #108,743

Date of Letter of Amendment: 19 June 2017

Site Instruction

The following information impacts the MTN-034/IPM 045 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. DAIDS sites are required to submit a LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). DAIDS sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB/EC correspondence should be retained in the site's regulatory files.

Summary of Revisions

This LoA does not impact the overall design or the study visit schedule for MTN-034/IPM 045.

The primary purpose of this LoA is to include one additional study recruitment site, the Makerere University – John Hopkins University Research Collaboration Clinical Research Site (CRS) (CRS#30293), to better distribute the recruitment burden across sites. This LoA also removes collection of a vaginal swab from two study visits, changes the frequency of administration of one behavioral assessment from a monthly to a quarterly visit procedure, changes the frequency in which the in-depth interviews (IDI) are conducted for those in the IDI subset from two to three, changes the timing of two behavioral questions from the enrollment visit to the screening visit, clarifies assent/consent form language related to the IDIs, clarifies one of the Exploratory endpoints for adherence, clarifies protocol language related to the location of study visits, updates the DAIDS Adverse Event (AE) Grading Table from Version 2.0 to 2.1, updates the Investigator Signature Page, updates the Protocol Team Roster, and makes other minor revisions to the protocol.

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

Detailed Listing of Revisions

The following revisions (#1-4) were made to include one additional study recruitment site, the Makerere University – John Hopkins University Research Collaboration CRS, to better distribute participant recruitment burden across sites:

1. The following additions have been made to the List of Abbreviations and Acronyms:

   MU-JHU Makerere University – John Hopkins University Research Collaboration
   NDA National Drug Authority (Uganda)

2. The following revision has been made to Appendix IV, Sample Informed Assent, last sentence of "Why is this study being done?" section:

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

3. The following revisions have been made to Appendix V, Sample Parent/Guardian Permission Form, and to Appendix VI, Sample Informed Consent Form, last paragraph of "Why is this study being done?" section:

   Regulatory bodies, including the US Food and Drug Administration (FDA), the Kenyan Pharmacy and Poisons Board (PPB), the Medicines Control Authority of Zimbabwe (MCAZ), **the Ugandan National Drug Authority (NDA)** and the South African Medicines Control Council (MCC)…

4. The following revisions have been made to Appendix V, Sample Parent/Guardian Permission Form, and to Appendix VI, Sample Informed Consent Form, "Who will be in this research study?" section:

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

The following revisions (#5-7) have been made to remove the collection of vaginal swabs for microbiota from two study visits and to change the frequency of the social harms/benefit assessment from a monthly to a quarterly schedule to reduce participant visit burden and study costs:

5. The following revisions have been made to Section 7.4.2, Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68, Table 10, Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68, sixth row under "Laboratory – Pelvic" component to remove vaginal swabs for microbiota from Visit 20, and fourth row under "Behavioral/Counseling" component to change the social harms/benefits assessment from a monthly to a quarterly schedule and only "if indicated" during the monthly visits:

Behavioral/Counseling	• Social harms/benefits assessment ∞*

Laboratory	**Pelvic**	• Vaginal swabs for microbiota∞ **(except on Visit 20)**

6. The following revision has been made to Section 7.4.3, Visit 23 - Week 72: Period 3 Product Use End/Early Termination Visit, Table 11, Visit 23 - Week 72: Period 3 Product Use End/Early Termination Visit, row under "Laboratory – Pelvic" component to remove vaginal swabs for microbiota from Visit 23:

Laboratory	**Pelvic**	~~• Vaginal swab for microbiota~~

7. The following revisions have been made to Appendix I, Table of Visits and Study Procedures, ninth row in the "Behavioral" section to change the social harms/benefits assessment from a monthly to a quarterly schedule and only "if indicated" during the monthly visits, and fifth row in the "Laboratory – Pelvic" section to remove vaginal swabs for microbiota from Visits 20 and 23:

		SCR: Visit 1	ENR: Visit 2	Visits 4-9, 11-16, 18-22	PUEV: Visit 23	Visits/Phone Contacts 3, 10, 17, 24
BEHAVIORAL						
Social harms/benefits assessment				~~X~~ ∞*	X	
LABORATORY						
PELVIC	Vaginal swabs for microbiota		X	∞ **(except on Visit 20)**	~~X~~	

The following revisions (#8-14) have been made to change the frequency in which IDIs are conducted for those in the IDI subset from two to three to capture qualitative data on all three product use periods, and to clarify in the assent/consent forms that more than one IDI may be conducted with participants in the IDI subset:

8. The following revisions have been made to Section 7.4.2, Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68, Table 10, Visits 4-9, Visits 11-16, Visits 18-22: Week 4 through Week 68, fifth row under "Behavioral/Counseling" component to move the IDI during the second product use period to an earlier visit and add one IDI during the third product use period:

Behavioral/Counseling	• In-depth interview (IDI) (Visits 5 ~~and 16~~**, 12 and 19** only) (subset of participants only)♦

9. The following revisions have been made to Section 7.7, Behavioral Evaluations, last sentence of last paragraph, to reflect the new IDI schedule:

   For example, a participant's first IDI may be scheduled between the Month 2 and Month 3 visit, the second IDI may be scheduled between the Month ~~12~~ **8** and Month ~~13~~ **9** visit, **the third IDI may be scheduled between the Month 14 and Month 15 visit,** and the FGD may be scheduled at a later date than their Month 18 visit to accommodate availability for both the site and for other study participants.

10. The following revisions have been made to Appendix I, Table of Visits and Study Procedures, tenth row in the "Behavioral" section to move the IDI during the second product use period to an earlier visit and add one IDI during the third product use period:

	SCR: Visit 1	ENR: Visit 2	Visits 4-9, 11-16, 18-22	PUEV: Visit 23	Visits/Phone Contacts 3, 10, 17, 24
BEHAVIORAL					
In-depth interview (IDI) (subset of participants only)			X♦ (Visits 5 ~~and 16~~**, 12 and 19** only)		

11. The following revisions have been made to Appendix IV, Sample Informed Assent, third bullet point of "What will be done at my visits?" section to allow for multiple IDIs with individual participants in the IDI subset:

    We may also ask you to do ~~an~~ **one or more** interview**s** with staff alone or in a group with other young women who are in the study. We may audio-tape ~~this~~**the** interview**(s)**. It is your choice if you want to do ~~this~~**the** interview**(s)**.

12. The following revision has been made to Appendix IV, Sample Informed Assent, last sentence of "Cost and Reimbursement" section to allow for multiple IDIs with individual participants in the IDI subset:

    If you are chosen to take part in the discussion**(s)** with staff alone or in a group…

13. The following revisions have been made to Appendix V, Sample Parent/Guardian Permission Form, and to Appendix VI, Sample Informed Consent Form, third bullet point of "What procedures will be done for this study?" section to allow for multiple IDIs with individual participants in the IDI subset:

    We may also ask your child/you to do ~~an~~ **one or more** interview**s** with staff alone or in a group with other young women who are in the study. She/You may choose not to do either. During the interview**(s)** or group discussion, we may ask her/you to discuss her/your use of the study products, her/your feelings about the study products and about being in the study, and other questions that can help researchers to better understand participants' experiences while in the study. We may audio-tape the interview**(s)** or group discussion.

14. The following revision has been made to Appendix V, Sample Parent/Guardian Permission Form, and to Appendix VI, Sample Informed Consent Form, last sentence of "Reimbursement" section to allow for multiple IDIs with individual participants in the IDI subset:

    If she/you is/are chosen to take part in the discussion**(s)** with staff alone or in a group…

The following revisions (#15-17) have been made to change the timing of two baseline behavioral questions from the enrollment visit to the screening visit to better capture participants' baseline responses to select questions that may be altered by the 2-month screening to enrollment window:

15. The following addition has been made to Section 7.3, Visit 1: Screening Visit, Table 7, Visit 1: Screening Visit, first row under "Behavioral/Counseling" component to add a targeted baseline behavioral assessment:

Behavioral/Counseling	• **Targeted baseline behavioral assessment**

16. The following revision has been made to Appendix I, Table of Visits and Study Procedures, sixth row in the "Behavioral" section to add a targeted baseline behavioral assessment at Screening:

	SCR: Visit 1	ENR: Visit 2	Visits 4-9, 11-16, 18-22	PUEV: Visit 23	Visits/Phone Contacts 3, 10, 17, 24
BEHAVIORAL					
Behavioral assessment	**X (Targeted)**	X	∞	X	

17. The following revisions have been made to Appendix IV, Sample Informed Assent, first bullet point of "What will be done at my visits?" section, and to Appendices V and VI, Sample Parent/Guardian Permission Form and Appendix VI, Sample Informed Consent Form, first bullet point of "What procedures will be done for this study?" section:

    - We will ask questions about your/your child's health and any medications you/she may be taking. We will also ask questions about your/her living situation to see if it affects your/her use of the study products**, and about your/her reasons for wanting to join this study and how you/she view/s your/her risk for getting HIV**.

The following revision (#18) has been made to clarify one of the Exploratory endpoints of adherence:

18. The following revision has been made to the Protocol Summary, third bullet point of third Exploratory Endpoint, and to Section 4.2, Summary of Major Endpoints, third bullet point of third Exploratory Endpoint:

    Returned VRs and pill ~~count~~ **bottles**

The following revisions (#19-22) have been made to clarify protocol language related to the location of study visits, to more explicitly distinguish between what DAIDS regards as the site (i.e., the CRS), and what the study participants will regard as the site (i.e., the clinic where they will be consented and undergo all study visit procedures) in the protocol:

19. The following revision has been made to Section 6.5, Retrieval of Study Product, first sentence of first paragraph:

    Study participants will be instructed to return all study products (unused FTC/TDF oral tablets or unused/used VR) to the ~~site~~**clinic** at each scheduled study visit.

20. The following revisions have been made to Section 7.1, Pre-Screening, third and last sentences:

    If deemed acceptable, during pre-screening interactions study staff may explain the study to potential participants and ascertain elements of presumptive eligibility, to be confirmed at ~~on-site~~**clinic** screening visits… Any participant who at any time expresses an interest in involving her current sexual partner and/or family members in discussions about study participation will be encouraged to bring them to the clinic ~~site~~, where…

21. The following revision has been made to Section 7.6, Final Contact, third sentence:

    Study sites may complete these contacts at the study ~~site~~**clinic** or at community-based locations…

22. The following deletion has been made to Section 13.4.1, Risks, FTC/TDF sub-section, last sentence of first paragraph:

    Participants taking FTC/TDF will be monitored closely for any side effects, and are asked to report all side effects to the study ~~site~~ clinician.

Additional minor modifications include:

23. Throughout the protocol the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was updated from Version 2.0, November 2014 to Version 2.1, March 2017.

24. The Investigator Signature Page has been revised to comply with updated DAIDS guidelines and newly required language.

25. Protocol Team Roster – Additions:

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26. Protocol Team Roster – Updates:

The University of Zimbabwe ~~University of California San Francisco Collaborative Research Program (UZ-UCSF)~~ **College of Health Sciences (UZCHS)** Clinical Trials Unit – Spilhaus CRS

The above information will be incorporated into the next version of the protocol at a later time if it is amended.