Letter of Amendment #01 to:

MTN-011

Phase 1 Evaluation of the Impact of Coitus on the Pharmacokinetics and Pharmacodynamics of Tenofovir 1% Gel Following Pericoital or Daily Gel Dosing

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Site Instruction

The following information impacts the MTN-011 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 also impacts the sample informed consent. Your IRB/EC will be responsible for determining the process of informing subjects 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 an 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. An 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-011. This LoA revises the protocol to allow for the use of intrauterine devices for contraception, provides guidance on the completion of follow-up visits and procedures, removes the requirement for participants to receive daily contacts from clinic staff, clarifies that use of systemic immune modulators will result in a permanent study product discontinuation, clarifies that drug will not be dispensed at Visit 7a, clarifies that cervical cytobrushes will be used for flow cytometry at one designated site and for PK at the other site, clarifies the male behavioral assessment schedule, permits the use of HIV-1 tests other than HIV-1 rapid tests, provides the risks associated with the insertion of an anoscope, and allows for the collection of associated health information with the samples stored for long-term storage and testing. In addition, typographical errors and protocol and informed consent discrepancies are corrected.

Text to be deleted is noted by strikethrough and text to be added is noted below in bold font.

Section 2: Implementation

1. Sections 5.2, Appendix IV and V, have been revised to remove the protocol restriction of intrauterine devices as an effective method of contraception.

   Section 5.2, 6 C:

   c. Must be currently using effective non-barrier contraception, other than a contraceptive vaginal ring ~~or intrauterine device~~, for at least three months prior to Screening (i.e., oral contraceptive, patch, injectable hormones, subdermal implants, **intrauterine device,** female or male sterilization) and intending to use this method for the course of the study.

   Appendix IV and Appendix V*,* Section *What Do I Have to Do if I Take Part In the Screening Exams and Tests*, second bullet, second sub-bullet, fifth item:

   o You must be on an effective form of contraception, other than a contraceptive vaginal ring ~~or intrauterine device (IUD)~~, for 3 months before the Screening and Enrollment visits approved for use in this study, including; oral contraceptive, patch, injectable hormones, subdermal implants, **intrauterine device**, female or male sterilization.

2. Section 6.6, *Retrieval of Unused Study Products,* first and second sentences are clarified:
   It is anticipated that for participants in Group 2, **one** unused applicator will be returned to the study site following each ~~consecutive administration at home~~ **period**, unless a replacement applicator is needed by the participant. Study participants in Group 2 will be instructed to return all unused applicators to the site. Unused applicators will be counted and documented, then sent to the pharmacy and placed in quarantine.~~.~~

3. Edits to Section 6.7, *Study Product Counseling and Adherence*, *Study Product Adherence Counseling* subsection, a new third paragraph has been added to specify that if a participant reports a prohibited practice, follow-up procedures will be at the discretion of the IoR:
   In the event a participant reports any of the aforementioned prohibited practices, continuation of the study visit procedures will be performed at IoR discretion.

4. Edits to Section 7.0, *Study Procedures*, first paragraph new third and fourth sentence:
   An overview of the study visit and evaluations schedule is presented in Appendices I and II. Presented in this section is additional information on visit-specific study procedures. **If a couple fails to comply with the protocol for a study visit (e.g., incomplete coitus), the IoR/designee may consult the study management team for procedure completion guidance. Visit procedures may be omitted at the discretion of the management team.** Detailed instructions to guide and standardize procedures across sites are provided in the MTN-011 SSP Manual available at www.mtnstopshiv.org/.

5. Edits to Section 7.5, *Group 2 (Multiple Dose Cohort) – Enrollment and Study Follow-up Visits*, last paragraph, is clarified to reflect that procedures will be performed on the male participant at Visit 9.
   At Visit 9 (Sampling), the couple returns the clinic after the female participant has administered the final dose of gel approximately 72 hours prior to the visit. Participants will return to the clinic and ~~the female participant will~~ undergo sampling procedures for the final time.

6. Edits to Section 7.9.2, *Product Adherence*, first paragraph, last sentence is modified:
   A reminder system is planned for this group during the home dosing phase, consisting of either ~~daily~~ reminder phone **calls** or text messages. **These contacts will ideally occur twice during each at-home product use period.**

7. Edits to Section 6.9 and 9.3 specify that the use of systemic immune modulators will result in a permanent study product discontinuation.

   Section 6.9, *Prohibited Medications and Practices*, third paragraph, first sentence:
   The use of **systemic** immune modulators is prohibited.

   Section 9.3, *General Criteria for Permanent Discontinuation of Study Product*, sixth bullet:
   - Report**ed** ~~of~~ use of ~~prohibited concomitant medications~~ **systemic immune modulators (prohibited medications** as **per** ~~described in~~ Section 6.9**)**

8. Edits to Table 13 and Appendix II removes the requirement of drug dispensation at Visit 7a, as product, for this period of use, will be dispensed at Visit 6.

   Table 13: Group 2, Visit 3a: Gel -1/Coitus, Visit 7a: Gel -72/Coitus, Female Participants column, bullets 1 and 2 modified, symbol added:

Component	**Female Participants**
Study Product Supply	• Provision of study product**×** • Study product use instructions**×**

×= Visit 3 a only

Appendix II, *Schedule of Study Visits and Evaluations: Group 2*, *Provision of study product* row, *Visit 7a* column, two rows have been modified:

	Visit 7a
	Gel -72/Sex
Study Product	
Provision of study product	~~X~~
Study product use instructions	~~X~~

9. Edits to Tables 8, 9, 14, 15, 16; Section 7.11, and Appendices I-IV, have been incorporated to allow for the use of cervical cytobrushes for flow cytometry at one site and for PK at the other site.

Tables 6 and 11, *Laboratory Row*, *Vaginal/Cervical/Penile* sub-row, Female participant column:

Component		Female Participants
Laboratory	**Vaginal/ Cervical**	• Cervical cytobrush – **Flow cytometry (at a designated site only)**

Tables 8, 9, 14 and 15, *Laboratory Row*, *Vaginal/Cervical* sub-row, Female participant column:

Component		Female Participants
Laboratory	**Vaginal/ Cervical**	• Cervical cytobrush – PK **or flow cytometry**

Table 16: *Pharmacokinetic Specimen Collection Schedule*, Specimens column, *Cervical cytobrush* row 3 of Group 1 and 2 are revised to read:

Cervical Cytobrush **(at a designated site)**

Section 7.11, *Network Laboratory* section, *Cervical* bullet, new third sub-bullet.

- Cervical
  - Biopsy tenofovir levels (NL Pharmacology Core)
  - Cytobrush for tenofovir levels (NL Pharmacology Core)
  - **Cytobrush for flow cytometry**

Appendix I and II, *Schedule of Study Visits and Evaluations*: Groups 1 and 2, *Laboratory* section:

	SCR
Cytobrush (FEMALE ONLY)	**X (from participants at a designated site only)**

Appendix IV and V, *What do I have to do if I Take Part in the Screening Exams and Tests?* section, *Study Staff will* section, third bullet, new fourth sub-bullet:

- **[Designated site ONLY] You will be asked to allow the study clinician to collect cells from your cervix using a brush. These cells will be used to help researchers understand the effect the drug and the act of sex have on the white blood cells in your genital tract after you have used the study product and had sex. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers.**

Appendix IV and V, *Enrollment and Study Procedures* section, *Clinical* procedures section, fourth bullet, fourth sub-bullet in Appendix V and fifth sub-bullet in Appendix IV:

- You will be asked to allow the study clinician to collect cells from your cervix using a brush, at visits following the use of study product and sex, if applicable. These cells will help ~~clinicians~~ **researchers** understand how much of the study drug was absorbed **or to help researchers understand the effect the drug and the act of sex have on the white blood cells in your genital tract. Because doctors do not yet understand enough about what these test results might mean, the results will only be seen by the researchers**.

10. Edits are made to the timing of behavioral assessments for male participants, specifically to; Table 9 and 15; Appendix I, II and VII.

Table 9 and 15, *Behavioral/Counseling* Row, Male participant column, first bullet:

Component	Male Participants
Behavioral/ Counseling	• ~~Conduct behavioral assessment~~

Appendix I, *Conduct behavioral assessment* row has been modified, in addition, a new row has been added:

GROUP 1	Visit 1	Visit 2a	Visit 2b	Visit 3a	Visit 3b	Visit 4a	Visit 4b	Visit 5a	Visit 5b	Visit 6a	Visit 6b	Visit 7a	Visit 7b

	SCR: NO GEL/ NO SEX	ENR: NO GEL/ SEX	Post Coital Samples (♀)	GEL -1/ SEX	Post Coital Samples (♀)	GEL -1/No Sex (♀)	Samples (♀)	Gel - 24/ Sex	Post Coital Samples (♀)	Gel -24/No Sex (♀)	Samples (♀)	Gel - 1/Sex /Gel +1	Post-Coital Samples/ Final Clinic
Conduct behavioral assessment **(FEMALE ONLY)**		X			X		X		X		X		X
Conduct behavioral assessment (MALE ONLY)		**X**											

Appendix II, *Conduct behavioral assessment* row has been modified, in addition, a new row has been added:

	Visit 1	Visit 2	Visit 3a	Visit 3b	Visit 4	Visit 5	Visit 6	Visit 7a	Visit 7b	Visit 8	Visit 9
	SCR	ENR	Gel - 1/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling (♀)	Provision of Product (♀)	Gel - 72/Sex	Post Coital Sampling (♀)	Provision of Product (♀)	Sampling/ Final Clinic
Conduct behavioral assessment **(FEMALE ONLY)**		X		X		X			X		X
Conduct behavioral assessment (MALE ONLY)		**X**									

Appendix VII: *Sample Informed Consent Document Group 2 Male Screening and Enrollment*, *Enrollment and Study Procedures* Section, second bullet, second sub-bullet:

- Answer questions about your participation in this study at ~~your final~~**some** clinic visit**s**, some of these questions may be asked on a computer, the study clinic staff will provide you with instruction prior to using the computer

11. An edit to Section 9.3, first bullet, has been incorporated to permit the use of HIV-1 tests other than rapids.
    - Indeterminate or positive HIV-1 ~~rapid~~ test

12. Section 10.5, new third paragraph following the bullets:
    ***Note: Couples that are not evaluable (based on the definition above) may provide evaluable data at some of their visits which can be considered for analysis.**

13. Edits to Section 13.4.1, Risks and Appendices IV and V modified to account for risks associated with the planned anoscopy and rectal sponge collection.

    Section 13.4.1, *Risks,* fourth paragraph modified*:*

    During the genital and pelvic examination male and female participants may feel mild pressure, discomfort and/or embarrassment. **Insertion of a lubricated anoscope will likely cause some discomfort. There is the risk of mild discomfort and pressure in addition to a slight risk of bleeding with the insertion of rectal sponges.**

    Appendices IV and V, *Sample Informed Consents for Female Participants* in Groups 1 and 2, *Risks and/or Discomforts* section, a new paragraph was added:

    <u>Risks of Anoscopy and Rectal Sponge Collection:</u> You may experience minor discomfort and pressure during insertion of the anoscope and sponge. In some cases, a small amount of bleeding may occur.

14. Edits to Appendices IV, V, VI, VII *Sample Informed Consents* for Male and Female participants in Groups 1 and 2, Storage and Future Testing of Specimens section, first paragraph has been modified to allow for the collection of associated health information along with samples.

    <u>Storage and Future Testing of Specimens</u> **<u>and Associated Health Information</u>**

    There might be a small amount of blood and other biological specimens left over after we have done all of the study related testing after your study visits. We would like to ask your permission to store your blood and other biological specimens ~~for testing in future studies~~ **along with associated health information for future research**. **This health information may include personal facts about you such as your race, ethnicity, sex, medical conditions and your age range.** You can still enroll in this study if you decide not to have blood and other biological specimens **and associated health information** stored for future studies. If you do not want blood and other biological specimens stored, we will destroy the left over specimens. Any future studies that may be done will also have to be approved by an IRB.

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