Letter of Amendment #01 to:

MTN-020

DAIDS Document ID: 11840

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase 3 Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women

Version 1.0 / 28 September 2011
IND# 110,659

Letter of Amendment date: November 7, 2011

Site Instruction

The following information impacts the MTN-020 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.

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-020. The primary reason for this LoA is to clarify the timing of pelvic exam schedule, samples to be collected and tests to be completed on vaginal samples collected. Also the collection of plasma and testing for CD4+ T cell count and HIV-1 RNA PCR after seroconversion has been clarified. The Clinical Research Products Management Center (CRPMC) has been removed from the protocol as study product will not be routed through the CRPMC. Other minor edits to the List of Abbreviations and Acronyms and updates to the Protocol Team Roster have been incorporated.

With the exception of the modifications to the Protocol Team Roster, text to be deleted is noted by strikethrough and text to be added is noted below in bold font.

Detailed Listing of Revisions

1. The following updates are made to the Protocol Team Roster:

Added:

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2. Study products for MTN-020 will not be routed through the Clinical Research Products Management Center. Section 6.4.3, Accountability, first paragraph has been modified accordingly. In addition, the List of Abbreviations and Acronyms has been updated to reflect the protocol change:

   Section 6.4.3, Accountability:

   Each CRS Pharmacist of Record (PoR) is required to maintain complete records of all study products received ~~from the NIAID Clinical Research Products Management Center (CRPMC)~~ and subsequently dispensed. All unused study products must be returned to the MTN Pharmacist after the study is completed or terminated unless otherwise instructed by the MTN Pharmacist. The procedures to be followed are provided in the MTN-020 Pharmacy Manual.

   List of Abbreviations and Acronyms:

   ~~CRPMC~~ ~~Clinical Research Products Management Center~~

3. Edits are made to Table 4, *Screening Visit*, Table 5, *Enrollment Visit*; Table 6, *Follow-up Visits*; and Table 8, *Study Exit/Termination Visit* and Appendix I, and Appendix IV, *Sample Informed Consent Document (SCREENING)*, to clarify the timing of the pelvic exams and the schedule for Gram stain, Endocervical swab, and Vaginal fluid pH collection.

   Table 4: Screening Visit:

Screening Visit		
Component		**Procedures**
Laboratory	**Pelvic**	• Collect pelvic specimens – Rapid test for Trichomonas – **Gram stain** – **Endocervical swab** – Herpes lesion testing*† – Vaginal fluid pH~~*~~† – Potassium hydroxide (KOH) wet mount for candidiasis*† – Saline wet mount for *Bacterial vaginosis* (BV)*† – Pap smear interpretation*

* if indicated, † per local standard of care

Table 5: Enrollment Visit:

Enrollment Visit		
Component		**Procedures**
Clinical		• Update medical and menstrual history • Update concomitant medications • Provide contraceptives*† • Conduct a physical examination • Perform a pelvic exam*† • Disclosure of available test results • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*
Laboratory	**Pelvic**	• Collect pelvic specimens*† – ~~Gram stain~~ – Vaginal fluid pH*† – ~~Endocervical swab~~ – Rapid test for Trichomonas*† – Herpes lesion testing*† – KOH wet mount for candidiasis*† – Saline wet mount for BV*†

* if indicated, † per local standard of care

Table 6: Follow-up Visits: Monthly, Quarterly, Semi-Annually

Follow-up Visits: Monthly, Quarterly, Semi-Annually	
Component	**Procedures**
Clinical	• Review/update medical and menstrual history • Review/update concomitant medications • Provide contraceptives*† • Perform physical examination◔* • Perform pelvic examination for the collection pelvic specimens and to assess local safety ◗*† • Disclosure of available test results • Record/update AEs • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*

◔ = to be completed at all quarterly visits (Months 3, 6, 9, etc.), ◗ = to be completed at all semi-annual visits only (Months 6, 12, 18, etc.), * if indicated, † per local standard of care

Table 8: Study Exit/Termination Visit

Study Exit/ Termination Visit	
Component	**Procedures**
Clinical	• Review/update medical and menstrual history • Review/update concomitant medications • Provide contraceptives*† • Disclosure of available test results • Perform pelvic examination*† • Record/update AEs • Treat or prescribe treatment for UTIs/RTIs/STIs or refer for other findings*

* if indicated, □ per local standard of care

Appendix I: Schedule of Study Visits and Evaluations:

		SCR	ENR	Monthly Visits	Quarterly Visits	Semi-Annual Visits	PUEV	Study Exit/ Term. Visit
CLINICAL								
Perform a pelvic exam		X	~~X~~*†	*†	*†	X	X	*†
LABORATORY								
PELVIC	Rapid test for Trichomonas	X	*†	*†	*†	X	*†	*†
	Herpes lesion testing	*†	*†	*†	*†	*†	*†	*†
	Vaginal fluid pH	~~*†~~**X**	~~X~~*†	*†	*†	X	X	*†
	KOH wet mount for candidiasis	*†	*†	*†	*†	*†	*†	*†
	Saline wet mount for BV	*†	*†	*†	*†	*†	*†	*†
	Gram stain	**X**	~~X~~			X	X	
	Vaginal fluid			X	X	X	X	X
	Pap Smear interpretation	*					X	
	Endocervical swab	**X**	~~X~~			X	X	

X mandatory, * If indicated, † per local standard of care, ◊= for archive, ₪= required at Month 1

Appendix IV: Sample Informed Consent Document (SCREENING), *What Do I Have To Do If I Decide To Take Part In The Screening Exams and Tests*, *Screening Visit* subsection, first sentence has been modified:

- The study staff may also collect samples from your cervix for **testing, including** a "Pap test". […]

4. Section 7.5.1, *Participants Who Become Infected with HIV-1*, the first bullet has been replaced to allow for the collection of plasma and testing for CD4+ T cell count and HIV-1 RNA PCR at the first opportunity available to study staff after a positive rapid is observed, in addition Appendix V, *Sample Informed Consent (ENROLLMENT)*, has been updated to reflect the additional testing:

   Section 7.5.1, Participants Who Become Infected with HIV-1:

   - ~~The visit (scheduled or interim) at which the participant is given her Western Blot or HIV RNA/DNA test results confirming her HIV infection~~
   - **Upon each instance of positive HIV rapid test(s) during follow-up**

   Appendix V, *Sample Informed Consent (ENROLLMENT), If you become infected with HIV* subsection, first paragraph has been modified:

   > Your participation in this study will not cause HIV infection. However, there is always a chance that through sexual activity or other activities you may become HIV-positive. ~~In the event you become HIV-positive, study staff will counsel and refer you for medical care and other available services. You will continue to be counseled while you are in this study.~~ **If the HIV tests confirm that you have been infected with HIV, you will stop using the ring, but we will ask you to continue to come into the clinic for regularly scheduled visits for some of the study procedures.** You will have more **blood** tests **at 1, 3, 6 and every six months after your HIV infection is discovered** to find out which drugs would be **in**appropriate for your type of HIV-1 (HIV drug resistance)**, the amount of immune protection in your blood (CD4+ T-cell count), and the amount of HIV in your blood (viral load).** ~~If the HIV tests confirm that you have been infected with HIV, you will stop using the ring, but we will ask you to continue to come into the clinic for regularly scheduled visits for some of the study procedures.~~ You may be referred to other research studies. **If you join another study it may not be necessary to collect additional blood for testing. In the event you become HIV-positive, study staff will counsel and refer you for medical care and other available services while you are in this study.**

5. Edits to Appendix V: Informed Consent Document (Enrollment) clarify the testing planned for the vaginal fluid testing. These edits have been incorporated into the *WHAT WILL I HAVE TO DO IF I AGREE TO TAKE PART IN THIS RESEARCH STUDY* section:

   - Provide vaginal fluid samples:
     - To see how much study product is ~~absorbed~~**retained** by your ~~body~~**vagina and indicators of safety** at all of your study visits. ~~We will test these samples only in the event that you become infected with HIV~~

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