

Letter of Amendment #02 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

Letter of Amendment date: 19 April 2012

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 (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-020. This LoA corrects the Investigational New Drug (IND) number listed on the cover page, offers minor clarifications to Section 6.0, Study Product, affords the continuation of vaginal procedures in women who become pregnant, clarifies the timing of vaginal fluid collection, allows for additional tests to be completed on vaginal rings and allows for flexibility regarding the completion of quantitative behavioral assessments in participants who discontinue study product use. In addition, the protocol has been modified to allow for the completion of in-depth interviews and focus group discussions. Other modifications include, the incorporation of required language to accommodate the FDA Final Rule regarding trial registration within the Sample Informed Consent(s) and clarification of language in the Enrollment Sample Informed Consent. Minor edits to the List of Abbreviations and Acronyms along with 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.

Section 2: Implementation

1. The following edit has been made to the cover page of MTN-020:

IND# ~~440,659~~**108,743**

2. The following updates are made to the Protocol Team Roster-

Added:

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The following individual has been removed from the Protocol Team Roster: Liza Noonan, PhD.

3. Edits to Section 6.1, *Regimen*, second paragraph, second sentence, clarify that the maximum length of time a vaginal ring may be inserted in the vagina:

The VR should be worn for approximately 28 consecutive days at a time ~~but~~ **and it is recommended for** not more than 35 days before being replaced.

4. Edits to Section 6.4.3, *Accountability*, first paragraph, last sentence clarify the proper name for the MTN-020 Pharmacist Study Product Management Procedures Manual:

The procedures to be followed are provided in the MTN-020 **Pharmacyist Study Product Management Procedures Manual**.

5. Edits to Section 6.4.4, *Retrieval of Study Product*, Table 3: *Retrieval of Study Product*, second row, reflect product hold guidelines:

Permanent discontinuation due to severe (Grade 3 or higher) renal or hepatic toxicity	Within 5 working days
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6. Edits to Section 6.4.4, *Retrieval of Study Product*, fourth paragraph, clarify procedures for ring retrieval:

If prolonged use (greater than 35 days) of the study VR has occurred, **attempts should be made to contact the participant and retrieve the study product** ~~must be retrieved~~.

7. Edits to Section 6.4.4, *Retrieval of Study Product*, fifth paragraph, second sentence, clarify when study staff should arrange to collect the study VR if not retrieved at the Study Exit/Termination Visit:

If the participant does not bring her remaining supplies to this visit, study staff must arrange to retrieve the VR within **25** business days.

8. Edits have been made to Section 7.3, *Enrollment Visit (Day 0)* and Appendix I: *Schedule of Study Visits and Evaluations* to clarify that collection of vaginal fluid should occur at Enrollment:

Section 7.3, *Enrollment*:

Laboratory	Pelvic	<ul style="list-style-type: none"> Collect pelvic specimens <ul style="list-style-type: none"> Vaginal fluid
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Appendix I: *Schedule of Study Visits and Evaluations, Laboratory, Pelvic* subheading:

	<u>SCR</u>	<u>ENR</u>	<u>Monthly Visits</u>	<u>Quarterly Visits</u>	<u>Semi-Annual Visits</u>	<u>PUEV</u>	<u>Study Exit/Term. Visit</u>
Vaginal fluid		X	X	X	X	X	X

9. Edits have been made in Section 7.5.2, *Participants Who Become Pregnant*, second bullet, to allow for the continuation of vaginal procedures:
- Pelvic examinations, including vaginal fluid collection, after 24 weeks of pregnancy, **unless participants indicate comfort with continuing vaginal procedures. See SSP Manual for additional guidance.**
10. Edits have been made to Section 7.5.3, *Participants Who Temporarily Hold or Permanently Discontinue Study Product Use*, see new second paragraph:

In the event that a participant permanently discontinues study product early, the Adherence and Acceptability Assessments will be administered according to guidance provided from the protocol team, see MTN-020 SSP Manual for additional guidance.

11. Edits have been made to allow for the completion of in-depth interviews and focus group discussions with a subset of participants to the list of *Acronyms and Abbreviations*, Section 5, *Study Population*, Section 7.7, *Behavioral Evaluations*, 13.4.1, *Risks*, and Appendix V, *Sample Informed Consent Document (Enrollment)*:

The following text has been added to the list of *Acronyms and Abbreviations*:

IDI	in-depth interview
FGD	focus group discussion

Section 5, *Study Population*, after 5.4 *Co-enrollment Guidelines*, a new subsection has been added:

5.5 Selection of Participants for In-depth Interviews and Focus Group Discussions

A subset of participants will be eligible for participation in in-depth interviews or focus group discussions regarding their trial experiences and use of the study products as outlined in Section 7.7.

Section 7.7, *Behavioral Evaluations*, below the third bullet, the following text has been added:

In a subset of participants the aforementioned behaviors will be further explored via in-depth interviews (IDI) and focus group discussions (FGDs). Approximately 35-40 participants per site, who agree to participate in the subset, and who have been selected for either IDI and/or FGD participation, will be asked to complete up to three IDIs and/or one FGD at select sites.

Section 7.7, *Behavioral Evaluations, Adherence Assessments* subsection, a second paragraph has been added:

The IDI and/or FGD subset will discuss a range of topics with trained interviewers/facilitators, such as potential challenges to VR use (e.g., novelty of device, use during menses and sex, dual use with contraceptives, other reproductive issues), partner and significant others' knowledge of study

participation and reaction to VR use, other topics related to adherence to the VR, and special issues relevant to VR use and VR adherence (e.g., motivation to join the trial, timing and circumstances around early study and/or product termination, etc.).

Section 7.7, *Behavioral Evaluations, Acceptability Assessments* subsection, a second paragraph has been added:

The IDI and/or FGD subset may include discussion of the following topics with trained interviewers; perceived benefits of VR use, willingness to use VR in the future, and practical issues of VR use in the “real world” (e.g., access, storage, disposal, insertion and removal, etc.), community attitudes towards the product, and other topics of interest related to acceptability of the VR.

Section 7.7, *Behavioral Evaluations, Sexual activity, condom use and intravaginal practices* subsection, a second paragraph and a new subsection have been added:

The IDI and/or FGD subset may include discussion of the following topics with trained interviewers/facilitators; the impact of VR use on sexual activity, condom use, and intravaginal practices, and other topics of interest related to sexual activity, condom use, and intravaginal practices.

In-Depth Interview and Focus Group Discussion Procedures

The IDIs and FGDs will be conducted in an appropriate meeting room that is conducive to the number of participants, confidentiality and privacy, and the need to audio-record the session. The FGDs and IDIs will be conducted at a time and location that allows for a neutral and comfortable environment. IDI and FGD participants will be greeted and staff will be available to fully explain the IDI and FGD process and answer any questions. The facilitator will then initiate the IDI and/or FGD by first explaining that the session will be audio-recorded and later transcribed and, if necessary, translated. Ground rules for conduct will be described (e.g., no interruptions, cell phones, confidentiality). The facilitator will then conduct the session by following the appropriate IDI or FGD guide. IDI and FGDs guides will be structured, but will allow opportunity for probing and exploration of spontaneously generated themes. Participants in the FGDs will be asked to use pseudonyms for themselves and for anyone they may talk about. A staff member will take notes during the session as a back-up to the audio-recording, and to record non-verbal information. The audio recording, notes, and analyses from these materials will be kept confidential.

Section 13.4.1, *Risks*, new seventh paragraph:

Participation in research includes the risks of loss of confidentiality and discomfort with the personal nature of questions. Participants who participate in the FGDs may disclose what other participants said during the discussion. All FGD participants will be asked and strongly encouraged to respect each other’s confidentiality. Furthermore, all FGD participants will be asked to use pseudonyms for themselves and for anyone they may talk about during the course of the FGD.

Section 13.6, *Participant Confidentiality*, second paragraph, the sentences were added after the sixth sentence:

All digital audio files will be stored on password-protected computers. Audio files will be transcribed. Please see SSP for guidance regarding audio file destruction.

Appendix V: *Sample Informed Consent Document (Enrollment), WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE ASPIRE STUDY?*, immediately preceding the *If you leave the study early, you will be asked to complete a final evaluation* subsection the following text has been added:

[Sites participating in the IDI and FGD Subset please insert the following language:]

Additional Study Activities (Optional)

You may also be asked to participate in a few optional study activities. If you choose to participate, you will be asked questions about your use of the ring, your preferences and opinions, your experiences with using the ring during sex, and any problems you may have had using the ring. Approximately 35-40 women at this site will be asked questions either in a group or individually. If you are asked and decide to accept to participate in these additional study activities, you will be compensated for your time and effort. You do not have to agree to participate in these activities to join this study. The interviews will be audio-recorded to make sure to record your words exactly

how you said them. The voice recordings will be destroyed as soon as the audio recording has been typed and checked. The audio recording, notes, and analyses from these materials will be kept confidential and will only use study numbers or fake names. This means that no one other than the MTN-020 study team will have access to your responses. The information that links you to the research materials will be kept in a secure location that will be accessed only by members of the MTN-020 study team for the purposes of this research.

In-depth Interview(s) and Group Discussions

You may be asked to participate in one, two, or three interview(s) with a trained staff member or you may be asked to participate in a group discussion with other study participants about opinions that you or other participants have. If you choose to participate, you will be asked to discuss your use of the study product, your feelings about the study product and trial participation, and other questions that can help researchers to better understand participants' experiences while taking part in the study. These discussions will last about one hour.

Initials & Date

Yes, I agree to participate in in-depth interviews or group discussions

Initials & Date

No, I do not want to participate in in-depth interviews or group discussions

Appendix V: *Sample Informed Consent Document (Enrollment)*, *WHAT DO I HAVE TO DO IF I DECIDE TO TAKE PART IN THE ASPIRE STUDY?* section, *Other possible risks* sub-section, the following text has been added:

[Sites participating in the IDI and FGD Subset please insert the following language:]

If you choose to participate in the group discussion, other participants will hear what you say. We will not reveal your full name to other participants. We will also ask every participant not to tell anyone outside of the group what any person said during the discussion. While it is not at all likely that your discussion will be made public, we cannot guarantee that everyone will keep the discussion private.

12. Edits have been made to Section 6.5, *Adherence Counseling and Assessment*, Section 7.4.1, *Monthly, Quarterly, Semi-Annual Study Visits*, Section 7.4.2, *Product Use End Visit (PUEV)*, Section 7.9, *Laboratory Evaluations*, Appendix I: *Schedule of Study Visits and Evaluation*, Section 10.9.2, *Adherence* and Appendix V: *Sample Informed Consent Document (Enrollment)* to allow for additional testing on returned vaginal rings:

Section 6.5, *Adherence Counseling and Assessment*, *Assessment* sub-section, new second paragraph:

Laboratory testing may be performed on returned vaginal rings to assess participant adherence.

In Section 7.4.1, *Monthly, Quarterly, Semi-Annual Study Visits*, Table 6: *Follow-up Visits: Monthly, Quarterly, Semi-Annually* and Section 7.4.2, *Product Use End Visit (PUEV)*, Table 7: *PUEV, Laboratory, Pelvic* sub-section a new line item was added:

- **VR adherence assessment(s), if indicated**

Section 7.9, *Laboratory Evaluations*, new sub-section added:

Study Product

- **Study VR adherence assessment(s), if indicated**

Section 10.9.2, *Adherence*, new number 6 added:

- 6.) Returned vaginal rings may serve as an additional indicator of product adherence.**

Appendix I, *Schedule of Study Visits and Evaluations, Laboratory, Pelvic* subheading:

	SCR	ENR	Monthly	Quarterly	Semi-Annual Visits	PUEV	Study Exit/ Term. Visit
Study VR adherence assessment(s)			*	*	*	*	

Edits have been made to Appendix V: *Sample Informed Consent Document (Enrollment)*, *You will be asked to use a study vaginal ring; as part of using this ring you will:* fourth bullet:

- Return your vaginal ring to study staff. **Study researchers may keep this ring and run additional tests on it. These tests will help researchers better understand your ring use.**

13. The following text has been added to the Screening and Enrollment Sample Informed Consent after the Research-Related Injury section to maintain compliance with the Food and Drug Administration (FDA) Final Rule to include trial registration information within the informed consent documents:

[Sites to insert where appropriate.] A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Web site at any time.

14. Edits have been made to Appendix V: *Sample Informed Consent Document (Enrollment)*, the *Consent for Off-Site Visits* section, second paragraph last sentence (these edits correct a typographical error in the text):

You can withdraw your consent for ~~the storage and future testing of specimens~~ **off-site visits** at any time by providing your request in writing to the person in charge of this study.

15. A typographical error has been corrected in Appendix V: *Sample Informed Consent Document (Enrollment)*, final signature block:

Sentence right before the signature block: If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to ~~have the~~ **participate in this study**, please sign your name below.

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