

LETTER OF AMENDMENT #01 TO:

MTN-025

A Phase 3B Open-Label Follow-on Trial to Assess the Continued Safety of and Adherence to a Vaginal Ring Containing Dapivirine in Women

Version 2.0, dated 16 December 2014

DAIDS Protocol #11985
IND #108,743

Date of Letter of Amendment: 11 April 2016

Site Instruction

The following information impacts the MTN-025 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 still 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-025.

The primary purpose of this LoA is to incorporate the primary results from IPM 027 (The Ring Study) and MTN-020 (ASPIRE), two trials that evaluated the safety and efficacy of the dapivirine vaginal ring (Ring-004). This LoA also adds two new exploratory objectives for characterizing ASPIRE participants who do not accept study product in MTN-025 and to explore alternative markers of product adherence, including participant self-report and analysis of hair samples. This LoA removes the protocol requirement to use FDA-approved HIV testing kit for HIV infection confirmation, allows for post-infection/pre-seroconversion testing of plasma samples, modifies the list of procedures that should stop after an HIV seroconversion, allows the use of audio files as source documents for in-depth interview data, explicitly allows for the concomitant use of oral tenofovir-based PrEP, updates the DAIDS Adverse Event (AE) Grading Table from Version 1.0 to 2.0, updates the risks associated with the dapivirine vaginal ring, updates DAERS contact information, 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 (#1-13) incorporate primary results from IPM 027 (The Ring Study) and MTN-020 (ASPIRE), including edits related to the start of MTN-025 implementation being contingent upon those two studies' findings.

1. In Section 2.1, Microbicides and Human Immunodeficiency (HIV) Prevention, after the second sentence in the fifth paragraph:

The results from two recently completed Phase 3 safety and efficacy trials of the dapivirine VR, MTN-020 (ASPIRE) and IPM 027 (the Ring Study), both of which found the VRs to be safe and effective in reducing HIV-1 infection in healthy female adults in sub-Saharan Africa when used for one month and replaced monthly, would indicate the advisability of initiating ~~Initiation of the MTN-025 study of the dapivirine VR as an open-label extension of MTN-020 (ASPIRE). will be contingent upon demonstration of the safety and efficacy of the product in the ongoing MTN-020 (ASPIRE) study. The specific level of effectiveness required to trigger activation of the MTN-~~

025 study will be decided upon following discussions with key stakeholders including regulatory authorities, community representatives, and sponsoring agencies.

2. A new, **Extended Safety and Efficacy**, sub-section was created in Section 2.4.1, *Clinical Studies of Dapivirine Vaginal Rings*, above the twelfth paragraph in the Safety subsection that starts "In March of 2012, IPM 027,":

Extended Safety and Efficacy

In March of 2012, IPM 027, also known as The Ring Study, was initiated. IPM 027 ~~is~~**was** a randomized, double-blind, placebo-controlled efficacy and long-term safety study that ~~will enroll 1,650~~ **enrolled 1959** healthy, HIV-uninfected women, ages 18-45. **Approximately 1762 women in South Africa and 197 in Uganda were randomized in a 2:1 ratio to receive either a dapivirine ring or a placebo ring.** ~~The study is being conducted in South Africa and Uganda.~~ Study participants ~~will use~~**used** either the dapivirine ring or the placebo ring every four weeks over approximately two years. The main goals of The Ring Study ~~are~~**were** to evaluate the long-term safety and efficacy of the dapivirine ring for the prevention of HIV-1 as compared to a placebo ring, when used by healthy, HIV-negative women over a two-year period. Additional goals included measuring the incidence of curable STIs, HIV-2 and pregnancy; monitoring ring acceptability (how well women liked using the ring) and adherence (if women used the ring as intended) as reported by the study participants; and tracking the development of any HIV-1 drug resistance in participants who ~~become~~**became** HIV positive during the study. ~~The study is anticipated to conclude in 2015/2016.~~

The median age at enrollment was **25 years**, and **91%** were unmarried. **At the data cut-off point, the total number of person years of follow-up was 2805, and 761 women had completed the two year follow-up period. A total of 133 post-randomization HIV-1 infections occurred: 77 among women assigned to dapivirine ring (incidence 4.08 per 100 person-years) and 56 among women assigned to placebo (incidence 6.10 per 100 person-years). Dapivirine vaginal ring reduced the risk of HIV-1 infection by 30.7% (95% CI: 0.90-51.5%; p=0.0401) relative to placebo. A 37.5% (95% CI: 3.5-59.5%) reduction in HIV-1 infection was observed in a subgroup analysis of women older than 21 years. Product-related AEs included metrorrhagia, menometrorrhagia, pelvic discomfort/pain, suprapubic pain and application site pain. There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms. Further, there was no overall difference between NNRTI resistance profiles.**

MTN-020, A Study to Prevent Infection with a Ring for Extended Use (ASPIRE), ~~is~~**was** a Phase 3 clinical trial designed to assess the efficacy and safety of a ring containing 25 mg of dapivirine for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled trial ~~is being~~**was** conducted in HIV-uninfected women, between the ages of **18 and- 45**. A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe ~~have~~ enrolled in the trial. Participants replaced the ring monthly for a minimum of one year. MTN-020 ~~aims~~**aimed** to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among healthy, sexually active, HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 included the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquired HIV-1 infection, and establishing steady state drug concentrations in the study population. ~~The study is anticipated to conclude in 2015.~~ **Results were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) February 2016 (Abstract #109LB) and published in the New England Journal of Medicine (N Engl J Med. Epub 22 Feb 2016. DOI: 10.1056/NEJMoa1506110).**

A total of 168 HIV-1 infections occurred: 71 among those assigned the dapivirine vaginal ring and 97 among those assigned the placebo ring (incidence 3.3 and 4.5 per 100 person-years, respectively). Dapivirine ring resulted in a 27% (95% CI: 1-46%, p=0.046) relative reduction in HIV-1 incidence overall and a 37% (95% CI: 12-56%, p=0.007) reduction in an analysis defined early in the study excluding data from two study sites with lower retention and adherence. In pre-defined as-randomized subgroup analyses, HIV protection differed significantly by age, with a 61% reduced risk of HIV for women ≥ 25 years [CI: 32%, 77%] p<0.001, and 10% reduced risk for women < 25 years (CI: -41%, 43%) p=0.64. A post-hoc analysis was conducted to further explore this result, which indicated that a 56% (95% CI: 31-71%, p<0.001) reduction among women older than 21 years of age, and no HIV-1 protection for women aged 18-21, with objective markers of adherence lower in this subgroup compared to women older than 21. The rate of adverse events was similar between study arms as was the frequency of antiretroviral resistance in those who acquired HIV-1.

There were no statistically significant differences in the frequency of the primary safety endpoints between the study arms or in other adverse events commonly detected in the study population. Incident sexually transmitted infections occurred at a similar rate in the two study arms. Finally, among those acquiring HIV-1, detection of non-nucleoside reverse transcriptase inhibitor mutations did not differ by study arm (8/68 assigned dapivirine and 10/96 assigned placebo, p=0.80).

The dapivirine ring was safe and effective in preventing HIV infection in both ASPIRE and The Ring Study. Results suggest the dapivirine ring could be an important HIV prevention option for women at risk of HIV infection.

3. The following revisions have been made to Section 2.7.1, Study Design, after the first sentence in the first paragraph:

~~Upon demonstration of the safety and effectiveness of~~ **Given that** the dapivirine VR **was found to be safe and effective** in the MTN-020 **study**, implementation of the follow-on trial, MTN-025, will commence

4. The following revisions have been made to Protocol Summary, Study Design:

~~Following demonstration of safety and efficacy of~~ **Given that** the dapivirine vaginal ring **was found to be safe and effective** in the MTN-020, eligible MTN-020 participants will be offered enrollment into MTN-025, a trial designed to obtain additional safety and adherence data in women.

5. The following revision has been made to Section 2.7.1, Study Design, fourth paragraph:

~~[...] (Ring-004) when inserted monthly in healthy, HIV-uninfected, not pregnant, sexually active research-experienced women should efficacy be demonstrated in MTN-020.~~

6. The following revisions have been made to Section 4.1, Identification of Study Design, first sentence:

~~The MTN-025 trial, HOPE, is a multi-site, open-label, Phase 3B trial that will be implemented if the dapivirine VR is found to be a safe and an effective HIV prevention method in the MTN-020 trial.~~

7. The following revisions have been made to Section 5.1, Selection of the Study Population, first sentence:

~~If safety and efficacy of the dapivirine vaginal ring are demonstrated in MTN-020 (ASPIRE); MTN-025 (HOPE), will be~~ **is being** implemented as a follow-on trial **to MTN-020 (ASPIRE), which demonstrated safety and efficacy of the dapivirine VR.**

8. The following revisions have been made to Section 13.4.2, Benefits, first sentence of first paragraph:

~~MTN-025 (HOPE) will only be implemented if~~ **Given that** the dapivirine vaginal ring as tested in MTN-020 (ASPIRE) **was** found to be safe and effective, ~~therefore,~~ participants in the HOPE study will experience the direct benefit of using a product that has been found to be safe and effective in preventing HIV acquisition and will be considered for potential regulatory approval.

9. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Informed Consent sub-section, after the second sentence of the first paragraph:

~~The research study you participated in, MTN-020: (ASPIRE), A Study to Prevent Infection with a Ring for Extended Use, showed that the dapivirine vaginal ring can reduce the chances of HIV-uninfected women from getting the HIV virus by [SITES TO INSERT: from X to X percent].~~ **prevented approximately one third of HIV infections. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented.** The study also learned that the dapivirine vaginal ring is ~~[SITES TO INSERT: safe (meaning that VR use they do not produce significant~~ **did not cause** health problems in persons who take them~~)]~~ when used by HIV-uninfected women. **In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results were similar to those in ASPIRE, demonstrating the dapivirine ring is safe, well-tolerated and effective, reducing HIV-uninfected women's chances of getting the HIV virus by approximately one third.** Only through the participation of volunteers in clinical research can the safety and effectiveness of medicine be better understood. ~~More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, you~~ are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study.

10. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), Informed Consent sub-section, after the first sentence of the first paragraph:

~~The research study you participated in, MTN-020: (ASPIRE), A Study to Prevent Infection with a Ring for Extended Use, showed that the dapivirine vaginal ring can reduce HIV-uninfected women's chances of getting the HIV virus by~~

~~[SITES TO INSERT: from X to X percent]~~ prevented approximately one third of HIV infections. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented. The study also learned that the dapivirine vaginal ring is ~~[SITES TO INSERT: safe (meaning that VR use it does not cause significant health problems)]~~ when used by HIV uninfected women. ~~More data is needed on the safety of the dapivirine vaginal ring. Because you took part in the ASPIRE study, y~~ In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results were similar to those in ASPIRE, demonstrating the dapivirine ring is safe, well-tolerated and effective, reducing HIV-uninfected women's chances of getting the HIV virus by approximately one third. You are being offered the opportunity to use the safe and effective dapivirine vaginal ring as part of this new study.

11. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), What do I have to do if I decide to take part in the MTN-025 study? sub-section titled "If you become infected with HIV", first sentence of second paragraph:

It may be necessary, depending upon local and national health requirements, for study staff to report diseases, including HIV, identified among MTN-020 ~~(ASPIRE)~~ **(HOPE)** study participants.

12. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), New Information sub-section, third and fourth sentence of the first paragraph, and second sentence of the second paragraph:

~~[SITES TO INSERT MTN 020 DATA HERE]. In addition to being tested as part of the ASPIRE trial, the ring was also tested in IPM 027. IPM 027 results will be provided to participants when they become available.~~

The HIV prevention researchers working on ~~this~~ MTN-025 (HOPE) are committed to sharing any data with you that becomes available, regardless of the product, if it is found to be effective in preventing the transmission of HIV.

13. The following revisions have been made to Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Purpose of the Decliner Population sub-section, after the first sentence:

~~MTN-025, is a study that provides former ASPIRE participants with~~ **eligible women** access to the dapivirine vaginal ring, a product that has been shown to reduce the chances of women from getting the HIV virus by. ~~[To be updated: X to X percent].~~ **MTN-020: (ASPIRE), A Study to Prevent Infection with a Ring for Extended Use, showed that the dapivirine vaginal ring prevented approximately one third of HIV infections were prevented. Among women older than 21, who used the ring more consistently than younger women, more than half of HIV infections were prevented.** The study also learned that the dapivirine vaginal ring is ~~[To be updated: safe (meaning that #VR use does not produce significant cause health problems), in persons who take it].~~

The following revisions (#14-37) have been made to add a new exploratory objective: characterization of participants who do not accept study product and to make the necessary changes in the protocol to satisfy the objective/endpoint:

14. The following bullet point items have been added to Protocol Summary, Exploratory Objectives, and to Section 3.3, Exploratory Objectives, to add the one new exploratory objective:

6. To characterize the MTN-020 participants who do not accept study product in MTN-025

15. The following bullet point items have been added to Protocol Summary, Exploratory Endpoints, to add the one new exploratory objectives' endpoints:

6. Characterization of MTN-020 participants who do not accept study product in MTN-025
- **Participant report of the factors that led to her decision to not accept study product**

16. The following revision has been made to Protocol Summary, Study Regimen, to clarify that HOPE participants have a choice regarding whether to accept study product:

Participants will ~~receive~~ **be offered** a silicone elastomer vaginal matrix ring containing 25 mg of dapivirine to be replaced each month for ~~a total period of~~ **approximately** 12 months of use.

17. The following revision has been made to Section 6.1, Regimen, first two sentences, to clarify that HOPE participants have a choice regarding whether to accept study product:

All participants will ~~receive~~ **be offered** a vaginal ring containing 25 mg of dapivirine to be worn monthly. **Participants will be able to choose whether to insert** ~~One new ring will be inserted~~ each month.

18. The following revision has been made to Section 6.2, Administration, first sentence, to clarify that HOPE participants have a choice regarding whether to accept study product:

If they choose, ~~The participants~~ will self-insert the study VR monthly.

19. The following revisions have been made to the second and third paragraph within Section 6.4.2, Study Product Dispensing, to clarify that HOPE participants have a choice regarding whether to accept study product:

~~During each of the monthly clinic visits participants will receive a new ring.~~ If the participant is unable to attend her next scheduled visit it is up to the discretion of the loR to provide **provision of an additional ring(s) may be provided at the discretion of the loR as permitted in the SSP.** All such circumstances must be documented fully by the loR/designee as described in the MTN-025 SSP Manual.

When participants enter the quarterly follow-up phase, ~~they~~ **those who choose to use study product** will be dispensed three rings at each study visit or be given the option of returning to ~~the site pharmacy or the clinic (based on site dispensing capacity)~~ each month to obtain a new vaginal ring ~~each month~~ (e.g., if they do not feel comfortable having a supply of two additional unused rings at home). Participant’s preference regarding product dispensation and their choice will be documented **and updated as needed.**

20. The following revisions have been made to Section 7.3, Enrollment Visit (Day 0), Table 6, Enrollment Visit (Day 0), rows under “Study Product/Supplies” component to ensure that it is clear that study VR use instructions will only be offered to participants if the product is accepted and to allow ASPIRE participants to choose to use study product in MTN-025:

Study Product/Supplies	<ul style="list-style-type: none"> Provision of study VR use instructions* Provision of Offer and, if accepted, provide study VR(s)
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21. The following revisions have been made to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, rows under “Study Product/Supplies” component; and Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits, rows under “Study Product/Supplies” component, to allow ASPIRE participants to choose to use study product in MTN-025:

Study Product/Supplies	<ul style="list-style-type: none"> Provision of study VR use instructions* Provision of Offer and, if accepted, provide study VR(s)
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22. The following revisions have been made to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, only row under “Laboratory-Study Product” and second row under “Study Product/Supplies”; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits, only row under “Laboratory-Study Product” and second row under “Study Product/Supplies”; and Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12, only row under “Laboratory-Study Product” and second row under “Study Product”, to complete procedures as indicated for those participants who choose to use study product in MTN-025:

Study Product	<ul style="list-style-type: none"> Adherence assessment(s): Returned study VR(s)*
Study Product/Supplies	<ul style="list-style-type: none"> Removal and collection of used/unused study VR(s)*

23. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, second bullet point after second paragraph, Section 7.6.2, Participants Who Become Pregnant, first bullet point; and Section 7.6.3, Participants Who Temporarily Hold or Permanently Discontinue Study Product Use, first bullet point, to clarify that HOPE participants have a choice regarding whether to accept study product:

- ~~Provision of~~ **Offer and, if accepted, provide** VR, **product use** instructions, **and product** adherence counseling

24. The following bullet point has been added to Section 7.8, Behavioral Evaluations, after the first paragraph, to include assessment of the newly added exploratory endpoint of “participant report of the factors that led to her decision to not accept study product”:

- Motivations for using or declining to use study product while participating in this research study**

25. The following revisions have been made to Section 7.9, Adherence Counseling, first sentence, to clarify that HOPE participants have a choice regarding whether to accept study product:

Study product adherence counseling will be provided as a component of the Protocol Adherence Counseling to all study participants by site staff. **Messages will be tailored based on whether or not the participant chooses to accept study product.**

26. The following revisions have been made to Section 10.1, Overview and Summary of Design, second sentence of first paragraph, to clarify that HOPE participants have a choice regarding whether to accept study product:

A sample size of approximately 1000-2500 participants will be followed for approximately 13 months, with approximately 12 months of study product use **for participants who choose to use the VR.**

27. The following bullet points have been added to Section 13.5, Informed Consent Process, first bullet point after third paragraph, to accommodate MTN-025 participants who do not accept study product in MTN-025:

- **The importance of study product adherence to its effectiveness**
- **That all participants may choose not to use study product at any time and still take part in the study**

28. The following revisions have been made to Appendix I, Schedule of Study Visits and Evaluations, last row in the “Laboratory” section and second to fourth rows under “Study Product/Supplies” section for consistency with changes made in Section 7.0:

	<u>SCR</u>	<u>ENR</u>	<u>M. 1 and 2</u>	<u>Quarterly Visits</u>	<u>PUEV</u>	<u>Study Exit/ Term. Visit (~ 1 Month after the PUEV)</u>
Adherence assessment(s): Returned Study VR(s)			X*	X*	X*	
STUDY PRODUCT/ SUPPLIES						
Provision of study VR use instructions		X*	*	*		
Provision of Offer and, if accepted, provide study VR(s)		X	X	X		
Removal and collection of used/unused study VR(s)			X*	X*	X*	

29. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Study Product section, second sentence of first paragraph; and to Appendix V, Sample Informed Consent Document (Enrollment), Study Product section, second sentence of first paragraph, to clarify that ASPIRE participants will be offered the vaginal ring MTN-025:

~~Unlike ASPIRE, there is no placebo vaginal ring (a ring without the study medicine) in HOPE, so a~~ **All HOPE participants will receive be offered the use of a vaginal ring containing dapivirine.**

30. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Purpose of the Screening Tests and the Study, second sentence and to Appendix V, Sample Informed Consent Document (Enrollment), Purpose of the Study section, first sentence:

~~This research study will test if a vaginal ring containing the medicine dapivirine is used as directed by participants and found to be is safe in participants who attend clinic visits~~ **when provided on a three-monthly schedule.**

31. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, second and third sentence of first paragraph, to clarify that HOPE participants have a choice regarding whether to accept study product:

~~You will insert~~ **be offered a new vaginal ring to use, with a new ring to be inserted** monthly for approximately 12 months **of use.** For some participants, this period of time may be less, **for instance, if a participant enrolls in the study late or chooses not to insert the vaginal ring every month she is enrolled.** ~~s~~ **Study staff will** can provide you with an estimate of how long you will ~~use the~~ **be offered access to the ring. Study procedures will be similar regardless of whether or not you choose to use the ring.**

32. The following revision was made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, fifth sentence edited:

You will have a final study visit to check on your health ~~approximately 4 weeks after the final ring is removed.~~

33. The following revision was made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, You will have the following clinical procedures performed, pelvic exam bullet:

A pelvic examination ~~when the vaginal ring is removed for the final time.~~

34. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, first sentence preceding second bullet point list, to clarify that HOPE participants have a choice regarding whether to accept study product:

You will be **offered** ~~asked to use~~ a study vaginal ring **to use**.

35. The following sentence has been added to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, at the end of the fourth bullet point in the second set of bullet points, and at the end of the second and fourth bullet points in the fourth set of bullet points, to inform participants that they may receive drug use results:

You may receive these test results indicating your study product use if you choose to accept the vaginal ring.

36. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, first bullet point of third bullet point list, to accommodate MTN-025 participants who do not accept study product in MTN-025:

- **If you chose to accept a ring for use,** ~~Y~~your experience using the vaginal ring, including whether or not the ring was removed from or fell out of your vagina.

37. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions sub-section, first sentence in the second and third paragraphs, to reiterate that MTN-025 participants who choose not to use study product may still be selected for in-depth interviews and group discussions:

If you are asked to participate in a group discussion, you will be asked to discuss your use of the study product, your feelings about the study product and trial participation, your vaginal practices and other questions that can help researchers to better understand participants' experiences while taking part in the study, **whether you used the vaginal ring or not**. These discussions will last about one hour.

[...]

If you are asked to participate in an interview, 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, **and whether you used the vaginal ring or not**.

The following revisions (#38-43) have been made to add the new exploratory objective: To explore alternative markers of adherence and to make the necessary changes in the protocol to satisfy the objective/endpoint:

38. The following bullet point items have been added to Protocol Summary, Exploratory Objectives, and to Section 3.3, Exploratory Objectives, to add one new exploratory objective:

7. To explore alternative markers of adherence

39. The following bullet point items have been added to Protocol Summary, Exploratory Endpoints, to add the new exploratory objective endpoints:

7. Exploration of alternative markers of adherence

- **Hair dapivirine levels**
- **Self-reported product use**

40. The following table sub-section has been added to; Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits; Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12; and Section 7.4.4, Study Exit/Termination Visit, Table 10, Study Exit/Termination Visit, to include hair collection as a procedure at each visit:

Hair	<ul style="list-style-type: none"> • Collect hair – Hair sample for DPV testing and archive
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41. The following table sub-section has been added to Appendix I, Schedule of Study Visits and Evaluations to include hair collection as a procedure at each visit:

		<u>SCR</u>	<u>ENR</u>	<u>M. 1 and 2</u>	<u>Quarterly Visits</u>	<u>PUEV</u>	<u>Study Exit/ Term. Visit (~ 1 Month after the PUEV)</u>
HAIR	Hair sample(s) for DPV testing and archive			X	X	X	X

42. The following bullet point has been added to Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study? section, at the end of the fourth bullet point list, to include hair collection as a procedure at each visit:

- **You will also be asked to provide a hair sample to see how much dapivirine is being absorbed by your body. If you choose not to provide a hair sample, you can still participate in all other study activities. We will reconfirm the decision you make today at all study visits should you change your mind about hair collection.**

43. The following revisions have been made to Appendix V, Sample Informed Consent Document (Enrollment), Consent for Storage and Future Testing of Specimens, first, second, seventh and eighth sentences, to include hair samples in the list of specimen samples that may undergo further testing if any are left over after all MTN-025 related testing is completed:

blood, **hair**, vaginal fluid and cervical fluid samples

The following revisions (#44-45) have been made to update the risks associated with the vaginal ring

44. The following revision has been made to Section 13.4.1, Risks, General Subsection, fifth paragraph replaced to update the risks associated with DPV VR use:

~~Based on AEs reported among female participants in previous studies, dapivirine VRs may be associated with:~~

- ~~• Metrorrhagia~~
- ~~• Vaginal discharge~~
- ~~• Vaginal candidiasis~~
- ~~• Vaginitis bacterial~~
- ~~• Urinary tract infection~~

~~Please note: Study product risks will be updated when the safety and effectiveness data from ASPIRE are available.~~

Safety data were evaluated from two Phase 3 trials, MTN-020 (ASPIRE) and IPM 027 (The Ring Study), which enrolled a total of 4588 women, and results were reported in February 2016. No safety concerns were noted in DPV VR users as compared to placebo VR users.

45. The following revision has been made to Appendix V, Sample Informed Consent Document (Enrollment), Risks of Study Drugs has been removed as the risks associated with the Study Rings is now sufficient:

Risks of Study Drugs

~~Based on side effects reported among women in previous studies, dapivirine vaginal rings may be associated with:~~

- ~~• Vaginal bleeding at irregular intervals, particularly between your expected menstrual periods~~
- ~~• Vaginal or genital discharge~~
- ~~• Yeast infection~~

• Urinary tract infection

The following revisions (#46-52) have been made to remove the protocol requirement to use FDA-approved HIV testing kits for HIV infection confirmation and to allow for post-infection/pre-seroconversion testing of plasma samples.

46. Instances of “HIV seroconversion” have been changed to “HIV infection” in cases where it is associated with the new HIV testing methods. This change impacts Section 6.4.4, Retrieval of Study Product, second sentence of first paragraph; Section 6.4.4, Retrieval of Study Product, Table 4, Retrieval of Study Product, first and second bullets; Section 6.4.4, Retrieval of Study Product, fourth paragraph; and Section 10.8, Analysis of Secondary Endpoints, first sentence in the first paragraph.

47. The following revisions have been made to Section 7.2, Screening Visit, Table 5, Screening Visit; Section 7.3, Enrollment Visit (Day 0), Table 6, Enrollment Visit (Day 0); Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2; Section 7.4.2, Quarterly Visits (Months 3, 6, 9), Table 8, Quarterly Visits; Section 7.4.3, Product Use End Visit (PUEV), Table 9, PUEV, Month 12; Section 7.4.4, Study Exit/Termination Visit, Table 10, Study Exit/Termination Visit; and Appendix I, Schedule of Study Visits and Evaluations:

Blood	– HIV-1 testing serology
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48. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, after the second sentence in the first paragraph:

Participants are offered enrollment in MTN-015 (<http://www.mtnstopshiv.org/studies>) at the visit when **HIV testing seroconversion** confirmation test-results are discussed with the participant.

For those participants who choose to be maintained in MTN-025 follow-up, regardless of co-enrollment in MTN-015, protocol-specified procedures for MTN-025 will continue, except the following:

- HIV ~~testing~~serology, HIV pre- and post-test counseling

49. The following revisions have been made to Section 7.6.1, Participants Who Become Infected with HIV, second and third bullets in last bullet point list:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR will be performed at the clinic visit immediately following confirmation of an HIV-infection and every ~~three months~~ **scheduled visit** thereafter for the remaining follow-up period, or as indicated
- HIV-1 Genotyping (standard resistance testing) will be performed on the stored plasma closest to the time of ~~confirmed~~ HIV-1 infection.
- ~~†~~**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.

50. The following revision has been made to Section 7.6.4, Interim Visits, fifth bullet in bullet point list:

- For interim HIV counseling and testing in response to participant report of symptoms consistent with acute **HIV infection**~~seroconversion~~ or presumed exposure to HIV

51. The following revision has been made to Section 7.11, Laboratory Evaluations, Local Laboratory sub-section, fourth bullet point in second bullet point list (Blood):

- HIV ~~testing~~serology

52. The following revisions have been made to Section 7.12, HIV Infection (Secondary Endpoint) Determination, after the fourth sentence in the first paragraph:

~~All confirmatory testing is performed using FDA-approved test kits.~~
[...]

- The MTN LC will test Study Entry, PUEV, and scheduled Termination Visit specimens from a 10% random sample of participants enrolled at each site for evidence of HIV infection ~~using FDA-licensed tests.~~ [...]

- The MTN LC will test **plasma specimens collected at the Study Entry visit and the visit at which HIV infection was detected** ~~Seroconversion specimens~~ from all study participants identified by the local laboratories as having become infected with HIV during the study follow-up period. The LC will also test matched Study Entry and Follow-Up specimens from a random sample of uninfected participants (equal to the number of **infected participants** ~~seroconversions~~). Study Entry specimens are collected at participants' Enrollment Visit. ~~Seroconversion~~ **Post-infection** specimens are collected at the schedule specified in Section 7.6.1. ~~All specimens will be tested for evidence of HIV infection using FDA-licensed tests. For all HIV-infected participants~~ ~~seroconverters~~, Study Entry specimens also will be confirmed.

The following revisions (#53-54) have been made to accommodate for plasma sampling at follow-up Months 1 and 2 for DPV testing and archive.

53. The following text has been added to Section 7.4.1, Months 1 and 2, Table 7, Follow-up Visits, Months 1 and 2, under "Laboratory-Blood" component, to include collection of plasma for archive at Months 1 and 2:

Blood	– Plasma sample for DPV testing and archive
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54. The following revision has been made to Appendix I, Schedule of Study Visits and Evaluations, fifth row in the "Laboratory-Blood" section and superscript legend, to include collection of plasma for archive at Months 1 and 2:

	<u>SCR</u>	<u>ENR</u>	<u>M. 1 and 2</u>	<u>Quarterly Visits</u>	<u>PUEV</u>	<u>Study Exit/ Term. Visit (~ 1 Month after the PUEV)</u>
Plasma sample for DPV testing and archive		◇	X	X	X	X

X mandatory, *If indicated, [†]Per local standard of care, ◇ **For archive**

The following revisions (#55-56) have been made to make clear that oral tenofovir-based PrEP concomitant use is permitted in countries where it is available:

55. The following revisions have been made to Section 2.7.2, Incorporating Emergent Effective HIV-1 Prevention Strategies, to allow the use of oral Truvada for PrEP by participants in countries where it is licensed for that use:

~~As of June 2014, the United States was the only country where ARVs (the combination daily oral pill emtricitabine/tenofovir disoproxil fumarate [Truvada®]) are licensed for use as pre-exposure prophylaxis (PrEP). However, as candidate microbicides continue to demonstrate evidence of efficacy, the potential for one or more licensed HIV-1 prevention strategies in sub-Saharan Africa may soon become a reality. The HOPE Protocol Team will follow all relevant national policies regarding HIV-1 prevention and will actively consult with stakeholders in the event that an effective intervention is approved locally. In study countries where oral tenofovir-based ARVs are provided to participants by a health care worker as PrEP, use will be documented as a concomitant medication.~~ Consultation with target populations, policy makers, governments and other stakeholders will be ~~ongoing~~ **conducted as needed** throughout the duration of study implementation and participant follow-up by study leadership, Microbicide Trial Network (MTN) Leadership and the MTN Community Working Group (CWG) **as other products become available.**

56. The following sentence has been added to Section 6.5, Concomitant Medications, after the second sentence, to allow the use of oral Truvada for PrEP by participants in countries where it is licensed for that use:

Oral tenofovir-based ARV use is permitted if approved, available, and provided to participants by a health care provider as PrEP. Oral tenofovir-based ARV use will be documented as a concomitant medication.

The following revisions (#57-61) have been made to accommodate the planned method of data management of the audio files and transcription of these files:

57. Section 11.1, Data Management Responsibilities, second paragraph, has been revised to allow the use of audio files as source documents for in-depth interview data:

~~Transcriptions of interviews and group discussion files (if applicable) will be generated in the field and will be electronically transferred to RTI International using a secure File Transfer Protocol (FTP) site, where they will be~~

uploaded and managed using a qualitative software package. RTI International will act as a hub, and manage all data for the study. A convention for file naming will be developed, and all data will be labeled according to this process. ~~Original language and translated~~ **Transcripts** will be transferred to RTI International as they are completed. RTI International will save all versions of all files on a secure, password-protected server.

58. Section 11.2, Source Documents and Access to Source Data/Documents, fourth paragraph, has been deleted to allow the use of audio files as source documents for in-depth interview data:

~~Audio files will be transcribed and immediately destroyed following a transcription quality assurance check. The site IOR or designee will be responsible for ensuring that these files have been destroyed.~~

59. Section 13.6, Participant Confidentiality, eighth and ninth sentence in the second paragraph, has been revised to allow the use of audio files as source documents for in-depth interview data:

Audio files will be **translated and transcribed in English and securely stored**. Please see **SSP Manual** for guidance regarding ~~audio file destruction~~.

60. Appendix V, Sample Informed Consent Document (Enrollment), What Do I Have to Do if I Decide to Take Part in the MTN-025 Study?, In-depth Interview(s) and Group Discussions, third sentence of the third paragraph, has been deleted to allow the use of audio files as source documents for in-depth interview data:

~~The voice recordings will be destroyed as soon as the audio recording has been typed and checked.~~

61. Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Risks and/or Discomforts, last two sentences of the second paragraph, have been deleted to allow the use of audio files as source documents for in-depth interview data:

~~When the information on the audio recording is typed onto paper and fully checked, the recording will be destroyed. Study leaders will make sure this happens.~~

Additional minor modifications include:

62. List of Abbreviations and Acronyms has been revised to include the acronym for NIAID's Clinical Research Management System, CRMS:

CRMS

Clinical Research Management System

63. Throughout the protocol the DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events was updated from Version 1.0, December 2004 (Clarification dated August 2009) to Version 2.0, November 2014.
64. Protocol Team Roster- Updates: MTN Leadership and Operations Center (LOC) Protocol Development Manager's name has been updated to Beth Galaska. Jennifer M. Berthiaume's title has been updated to Clinical Data Manager. Danielle Crida's telephone number has been updated to +27-21-6505873
65. Protocol Team Roster- Removals: Arendevi Pather, Patrick Ndase, Karen Patterson, Cynthia Grossman, Katie Schwartz, Flavia Matovu Kiweewa.
66. Protocol Team Roster- Additions:

Brenda Gati Mirembe, MBChB, MSc Epidemiology
Site Investigator of Record
MU-JHU Research Collaboration
P.O. Box 23491, Kampala Uganda
Phone: +256 414 541 044/+256 772 881 922
Fax: +256 414 543 002
Email: bgati@mujhu.org

Portia Hunidzarira, MBChB
Site Investigator of Record
UZ-UCSF
15 Phillips Avenue, Belgravia
Harare, Zimbabwe
Phone: +263 4 704920
Fax: +263 4 704897
Email: phunidzarira@uz-ucsf.co.zw

Kailazarid Gomez, MPM
Sr. Clinical Research Manager
FHI 360
PO Box 21059
Durham, NC 27703 USA
Phone: 919-544-7040, Ext. 11282
Fax: 919-544-0207
Email: kgomez@fhi360.org

Melissa Peda, MPA
Clinical Data Manager
FHCRC – SCHARP
1100 Fairview Ave. North, LE-400
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7672
Email: mapeda@scharp.org

Jason Pan
Statistical Research Associate
FHCRC-SCHARP
1100 Fairview Ave. North, M2-C200
PO Box 19024
Seattle, WA 98109-1024 USA
Phone: 206-667-7180
Email: zpan@fhcrc.org

67. Section 7.1, Pre-Screening a new fourth sentence has been added to include the planned collection of reasons former MTN-020 (ASPIRE) participants do not enroll in MTN-025 (HOPE).

[...] Process information (e.g., number of potential participants contacted, number presumptively eligible) may be recorded and stored at the study site in the absence of written informed consent from potential participants, provided the information is collected in such a manner that it cannot be linked to potential participant identifiers. **Reason(s) for not enrolling former MTN-020 (ASPIRE) participants (e.g., unable to contact, ineligible based upon pre-screen, associated reasons for ineligibility, refusal, etc.) will be recorded.** At each site, procedures and documentation will comply with local IRB/EC requirements.

68. Section 7.6.1, Participants Who Become Infected with HIV, three bullets have been added after the fourth bullet following the second paragraph, to include plasma, hair and vaginal fluid collection in the list of procedures that would stop in the event of HIV seroconversion during the study:

- **Plasma collection for DPV testing and storage**
- **Hair collection**
- **Vaginal fluid collection**

69. Section 8.1, Safety Monitoring, has been updated to clarify the composition of the PSRT:

A sub-group of the Protocol Team, including the Protocol Co-Chairs, DAIDS Medical Officer, Protocol Safety Physician(s), and IPM Representative ~~and SDMC Clinical Affairs Safety Associate~~ will serve as the Protocol Safety Review Team (PSRT).

70. Section 8.2, Clinical Data Safety Review, has been updated to remove the Clinical Affairs staff designation:

Participant safety is also monitored at the Network level through a series of routine reviews conducted by the SDMC ~~Clinical Affairs staff~~, the PSRT, and study sponsors.

71. Section 8.3.1, Adverse Events, has been updated to remove the mention of the DataFax system:

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to “continuing at the end of study participation” ~~and the AE log form should be re-faxed to SCHARP DataFax.~~

72. Section 8.4.1, Adverse Event Reporting to DAIDS, has been revised to update the DAERS support contact information in case of DAERS-related queries, and to correct a number of acronym errors:

Requirements, definitions and methods for expedited reporting of AEs are outlined in Version 2.0 of the DAIDS EAE Manual, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>. For each study participant, ~~expedited~~ EAE reporting will be undertaken throughout the scheduled duration of follow-up, i.e., from the time of Enrollment through study termination.

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for expedited EAE reporting to DAIDS. In the event of system outages or technical difficulties, expedited EAEs may be submitted via the DAIDS EAE Form. **This form is available on the RSC website, <http://rsc.tech-res.com/safetyandpharmacovigilance/>.**

For questions about DAERS, please contact **NIAID Clinical Research Management System (CRMS) Support** at ~~DAIDS-ES~~ at ~~DAIDS-ESSupport@niaid.nih.gov~~ **CRMSSupport@niaid.nih.gov**. Site queries may also be sent from within the DAERS application itself.

Where DAERS has not been implemented, sites will submit expedited EAEs by documenting the information on the current DAIDS EAE Form. ~~This form is available on the RSC website, <http://rsc.tech-res.com/safetyandpharmacovigilance/>.~~ For questions about EAE reporting, please contact the RSC (DAIDSRSCSafetyOffice@tech-res.com).

73. Section 11.1, Data Management Responsibilities, has been updated to remove the mention of the DataFax system:

Study CRFs will be developed by the MTN SDMC in conjunction with the protocol team. Quality control reports and queries routinely will be generated and distributed by the SDMC to the study sites for verification and resolution. As part of the study activation process, each study site must identify all CRFs to be used as source documents. Study CRF data are transferred to the MTN SDMC, entered, and cleaned using the ~~DataFax~~ data management system.

74. The following revisions have been made to Appendix IV, Sample Informed Consent Document (Screening), Informed Consent section, second to last sentence of first paragraph; and to Appendix V, Sample Informed Consent Document (Enrollment), Informed Consent section, second to last sentence of first paragraph:

A total of 2629 women enrolled into MTN-020 (ASPIRE) ~~and all former ASPIRE participants who are eligible for MTN-025 (HOPE) may take part.~~ It is anticipated that approximately 1000 to 2500 ~~former ASPIRE~~ **eligible** participants will enroll in HOPE.

75. The following revisions have been made to Appendix VI, Sample Informed Consent Document (MTN-025 Decliner Population), Study Procedures sub-section, new third sentence was added to highlight that the in-depth Interviews are planned with a subset of participants only:

STUDY PROCEDURES

[...] If you agree to take part in this study, the interviewer will ask you some brief questions and write your responses on a form. **It is important you know that not all participants will take part in the IDI; most participants will complete a questionnaire only.** Multiple visits may be needed to complete the IDI and questionnaire(s). During the IDI, the interviewer will also ask in-depth questions, during which time notes may be taken and the conversation will be audio-recorded.

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