

**SUMMARY OF CHANGES
INCLUDED IN THE FULL PROTOCOL AMENDMENT OF:**

MTN-023/IPM 030

**Phase 2a Safety Study of a Vaginal Ring Containing
Dapivirine in Adolescent Females**

DAIDS Protocol #11927

IND #108,743

THE AMENDED PROTOCOL IS IDENTIFIED AS: Version 2.0 14 January 2015

Information/Instructions to Study Sites

The information contained in this protocol amendment impacts the MTN-23/IPM 030 study and must be forwarded to your Institutional Review Board (IRB)/Ethics Committee (EC) as soon as possible for their information and review. IRB approval is required before implementation of the modifications contained in this amendment. All IRB requirements must be followed.

Please file this Summary of Changes, Version 2.0 of the protocol and all associated IRB correspondence in your essential documents files for MTN-23/IPM 030.

Summary of Revisions

This amendment incorporates a previously issued Clarification Memo and a Letter of Amendment. To ease in the review process, all revisions are displayed below without distinction. A summary of revisions is provided below:

1. The Protocol Team Roster has been updated.
2. In the Protocol Summary and throughout the protocol, based upon a recommendation from the US Food and Drug Administration (FDA), updates were made to extend the length of follow-up to 6 months (24 weeks).
3. In Section 2, INTRODUCTION, background information is updated to incorporate recently released MTN-013 data and to reflect the new Investigator's Brochure.
4. In Section 3, STUDY OBJECTIVES, edits are made to reflect the extended length of follow-up.
5. In Section 4, STUDY DESIGN, updates were made to extend the length of follow-up to 6 months (24 weeks).
6. In Section 6, STUDY PRODUCT, edits are made for consistency with the extended follow up schedule.
7. In Section 7, STUDY PROCEDURES, has been edited to add in study visits at weeks 16, 20, and 24. Further, testing/sampling/behavioral assessments have been adjusted.
Please note: The note added within LoA #01 that permitted the collection of vaginal swabs in lieu of urine for Nucleic acid amplification test (NAAT) for Neisseria gonorrhoeae and Chlamydia trachomatis (GC/CT) has been further revised.
8. Section 10, STATISTICAL CONSIDERATIONS edits are made to adjust for the extended follow-up schedule.
9. Appendix I: Schedule of Study Visits is updated.
10. Appendix IV: Sample Informed Consent Form (Screening, Enrollment, and Long-Term Storage) has been updated to align more closely with the standard MTN Consent for Storage and Future Testing of Specimens and Related Health Data language.

11. Other minor updates, corrections, and clarifications are incorporated

With the exception of updates to the roster text to be deleted is noted by ~~strikethrough~~ and text to be added is noted below in **bold**.

Detailed Listing of Revisions to Version 2.0

1. *The following individuals have been added to the PROTOCOL TEAM ROSTER:*

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2. *Personnel information for the following individuals has been updated within the PROTOCOL TEAM ROSTER: Roberta Black, Cynthia Grossman, Bill G. Kapogiannis, Dianne M. Rausch, Lydia E. Soto-Torres, Lisa Levy, and Katherine Bunge.*
3. *The following individual has been removed from the PROTOCOL TEAM ROSTER: Sonia Gor*
4. *PROTOCOL TEAM ROSTER, MTN Network Laboratory underwent a name change*

MTN Network Laboratory (NL) Center (LC)

5. *Section 2, PROTOCOL SUMMARY, edits are made to lengthen the study duration:*

Study Duration: Accrual is expected to be completed in approximately ~~6-9~~**12** months per site. Each enrolled participant will be followed for approximately ~~43~~**25** weeks

Study Regimen: Participants will be randomized in a 3:1 ratio to receive either a silicone elastomer vaginal ring containing 25 mg of dapivirine or a placebo VR. The ring will be replaced every 4 weeks during the ~~42~~**24** week study product use period

6. *Section 2, PROTOCOL SUMMARY, The Primary, Secondary and Exploratory objectives were updated to reflect the extended study duration:*

Safety

To assess the safety of dapivirine (25 mg) administered via a silicone vaginal ring in HIV-uninfected adolescent females, when inserted once every 4 weeks during ~~42~~**24** weeks of study product use

Acceptability

To evaluate the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a ~~42~~**24** week period

Adherence

To evaluate adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females,

when inserted once every 4 weeks for a ~~12~~24 week period

Vaginal Microenvironment

Describe the genital microenvironment over ~~12~~24 weeks of study product use

7. *Section 1.3, MEDICAL OFFICERS, Contact information for Lydia Soto-Torres was changed.*
8. *Section 1.4, CLINICAL LABORATORIES, MTN Network & Pharmacology Laboratories underwent a name change.*
9. *Section 2.4.2, Condom Compatibility Studies of Dapivirine, information regarding the condom functionality studies was added:*

~~Chemical condom compatibility studies have not been conducted with the study VRs; however, a male condom compatibility study (IPM 029) is currently ongoing and a female condom compatibility study (IPM 033) is in development.~~ **Results from male and female condom compatibility studies, IPM 029 and IPM 033 respectively, are anticipated in 2014.**

Chemical compatibility studies with different dapivirine-containing gel formulations ~~were~~ **have been** conducted on the following types of condoms:⁵

The results of condom compatibility testing indicate that dapivirine-containing vaginal gel formulations (0.05%) have no deleterious effects on the integrity of male or female condoms, **as indicated by tensile condom properties tested pre- and post-treatment. Two clinical condom functionality studies (one with male condoms [IPM 029] and one with female condoms [IPM 033]) were conducted with a placebo vaginal ring (silicone elastomer ring containing no active ingredient). Results from both studies showed that the difference between the total clinical failure rate between condom use with the vaginal ring and condom use without the vaginal ring was less than the pre-defined non-inferiority margins (3% for the male condom study and 8% for the female condom study). Condom use was safe and well tolerated with vaginal ring use.**

Polyisoprene condoms were removed from this list.

10. *Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, the introductory paragraph was updated to reflect the new Investigator's Brochure:*

To date, ~~276~~ Phase 1 and Phase 1/2 clinical trials of dapivirine have been conducted:⁵

- ~~seven~~ **Eight** trials of dapivirine VRs (25 mg and 200 mg loads) in which ~~234~~ **469** participants were assigned to dapivirine VRs,
- ~~e~~**Eight** trials of dapivirine vaginal gel in which 491 participants used dapivirine vaginal gel,
- ~~a~~**And 41**~~eleven~~ trials of oral dapivirine among 211 participants.⁸² ~~Please note, MTN-013/IPM 026 is included in the study product count above.~~

Efficacy and safety results from MTN-020 and IPM 027 will be made available to MTN-023 participants if the MTN-023 trial is still ongoing.

11. *Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, Pharmacokinetics was updated to reflect the new Investigator's Brochure, and the sub-section title was also changed:*

Clinical Pharmacokinetics

Dapivirine vaginal rings

IPM conducted a 28-day safety and pharmacokinetics (PK) trial (IPM-018) in HIV-uninfected women using tin-catalyzed silicone matrix and reservoir rings containing 25 mg of dapivirine. The rings were found to be generally safe and well-tolerated with a promising drug release profile.¹³

IPM also conducted a 28-day trial (IPM-024) involving 16 healthy, HIV-uninfected, sexually abstinent women, between 18 and 40 years of age. The women were randomly assigned (1:1) to a dapivirine (25 mg) ring or a placebo ring for 28 consecutive days. Post-ring insertion (1.5 hour), quantifiable plasma dapivirine concentrations (lower limit of quantification (LLOQ) = 3.00 pg/mL) were observed.¹⁴ These concentrations showed a gradual increase over time, reaching a mean C_{max} of 355.0 pg/mL by Day 7 (median T_{max}).

The individual plasma dapivirine concentrations did not exceed 1 ng/mL, and were well below plasma levels at the maximum tolerated dose for oral treatment.

For dapivirine in vaginal fluids, quantifiable concentrations (LLOQ = 0.40 ng) were also observed 1.5 hours after ring insertion. Generally, maximum concentrations were reached earlier than in plasma. The highest concentrations were observed in the area near where the ring was placed (mean C_{max} : 79.9 µg/g; median T_{max} : Day 3), followed by the cervix (mean C_{max} : 66.6 µg/g; median T_{max} : Day 4). Dapivirine vaginal fluid concentrations were well above the reported in vitro IC_{50} (50% inhibitory concentration for virus replication) of 0.3 ng/mL in MT4 T cells and the concentration at which greater than 99% inhibition of integrated provirus was observed (3.3 ng/mL) in cervical tissue. On Day 28, prior to ring removal, the mean concentrations ($C_{pre-ring-removal}$) were 38.6 µg/g, 35.8 µg/g and 13.3 µg/g in the area of the ring, in the cervix and near the introitus, respectively.¹²

By Day 56 (final visit), the plasma dapivirine concentrations of all participants but one were below the LLOQ (3.00 pg/mL) and in all participants, vaginal fluid levels were below the LLOQ.

IPM-013 was a Phase 1, randomized, double-blind, placebo-controlled trial conducted over three months in 48 healthy, HIV-negative, sexually active women, 18 to 40 years of age in Belgium. This trial evaluated the delivery of dapivirine from the same ring as used in IPM-024 but over different periods of use and assessed local and systemic safety. Participants were randomized (3:1) to either active or placebo ring. Two groups completed the trial with varying lengths of use. In Group A, the VR was removed on Day 28, and a new ring was inserted on Day 31 for the next 28 days. In Group B, the initial ring was removed on Day 35 and a new ring was inserted on Day 38 for the next 21 days. Group B had a third ring inserted on Day 59; this ring was worn for 24 hours.

Compared to vaginal fluids, systemic exposure to dapivirine levels in plasma was low.¹⁵ Plasma concentrations did not exceed 553 pg/mL, while the highest vaginal fluid concentration obtained was 171 µg/g. Data suggest that dapivirine is readily released from the ring and absorbed into the surrounding tissue and into the bloodstream. Concentrations of dapivirine collected within 4 hours of first ring insertion showed quantifiable plasma (LLOQ = 3.00 pg/mL) and vaginal fluid (LLOQ = 0.4 ng) levels. Interestingly, extending the period the ring was worn from 28 to 35 days resulted in some reductions in vaginal fluid concentrations in the area of the ring (32.4 to 20.3 µg/g) and at the cervix

(27.8 to 18.5 µg/g), but levels were similar at the introitus (10.3 to 9.9 µg/g). These values remained at least 3000 times higher than the in vitro 99% inhibitory concentration (3.3 ng/mL) in cervical tissue following challenge with HIV-1BaL.

In all clinical trials of dapivirine vaginal rings and gels to date, dapivirine concentrations in plasma have been very low (less than 2 ng/mL) or undetectable after up to 84 days exposure. Plasma levels of dapivirine after vaginal exposure in clinical trials are 1000-fold lower than maximum plasma concentrations after oral administration of dapivirine (e.g. Cmax after 300 mg b.i.d. for 14 days was 2286 ng/mL).⁵

The clinical pharmacokinetic profile of Ring-004 in IPM 013 showed a rapid increase in plasma and vaginal fluid concentrations of dapivirine after ring insertion, resulting in maximum concentrations in plasma by Day 7 and in vaginal fluids between Day 1 and Day 14, after which concentrations decreased steadily over the remainder of a 28-day or 35-day ring use period. Plasma dapivirine concentrations did not exceed 1 ng/mL, and were therefore well below concentrations at the maximum tolerated dose (MTD) for multiple oral doses (300 mg b.i.d. for 14 days; plasma Cmax of 2286 ng/mL). For dapivirine in vaginal fluids, the highest concentration was observed in the area where the ring was placed, followed by the cervix, with the lowest concentrations near the introitus.

Data from post-use analysis of residual levels of dapivirine in Ring-004 (IPM 015, in which a ring was inserted once every 28 days over a 12-week period) indicate that, on average, 4 mg of dapivirine were released over approximately one month of ring use. The mean amounts of dapivirine remaining in the used rings were similar for Weeks 4, 8 and 12 (post-insertion), at 21.09 mg, 21.54 mg and 21.84 mg, respectively. No clear relationship (neither linear nor exponential) was observed between the residual amount of dapivirine and corresponding plasma concentrations (i.e. at scheduled ring removal). It would appear that plasma concentrations below approximately 200 pg/mL were generally associated with above-average ring residual amounts, while the residual amounts appeared relatively constant (at levels between approximately 20 and 22 mg) for plasma concentrations above this value (200 pg/mL).

12. Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, Safety, Table 2 was updated to reflect the new Investigator's Brochure:

Table 12: Clinical Phase I/II Trials of Dapivirine Vaginal Rings

Trial Details			Number of Participants				
Trial Number	Description	Country	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25 mg)	Ring-004 matrix** (25 mg)	Placebo Ring
IPM 001	Safety and PK in women; 7 days	Belgium	12	--	--	--	12 (crossover)
IPM 008	Safety and PK in women; 7 days	Belgium	--	10	--	--	3
IPM 013	Safety and PK in women; 56/57 days	Belgium	--	--	--	36	12

Trial Details			Number of Participants				
Trial Number	Description	Country	Ring-001 reservoir (200 mg)	Ring-002 reservoir (25 mg)	Ring-003 matrix* (25 mg)	Ring-004 matrix** (25 mg)	Placebo Ring
IPM 015	Safety and PK in women; 84 days	Multiple Countries in Sub-Saharan Africa	--	--	--	140	140
IPM 018	Safety and PK in women; 28 days	Belgium	--	8	8	--	8
IPM 024	Safety and PK in women; 28 days	Belgium	--	--	--	8	8
MTN-013/ IPM 026***	Safety and PK in women	United States				12	12
IPM 028	Drug-drug Interaction (miconazole nitrate); 28 days	Belgium				36	0
IPM 034	Safety and PK in women; 7, 14, 28, 56, or 84 days	Belgium				40	0
TOTAL participants			12	18	8	172	195

*Tin-catalyzed matrix ring.

**Platinum-catalyzed matrix ring

*** MTN-013/ IPM 026 was the first in human clinical trial of a vaginal ring containing maraviroc alone, dapivirine alone or a combination of the two (dapivirine/maraviroc) **compared to placebo**. The dapivirine VR arm included 12 participants. **It should be noted, however, that the dapivirine VR was similar to Ring-004, but of slightly different composition.**

13. Section 2.6.1, *CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS*, Safety, safety data for the Ring-004 studies was updated to reflect the new Investigator's Brochure:

‡**Ring-004**, the current formulation, ~~Ring-004~~, is a dapivirine **matrix** VR containing 25 mg of drug substance dispersed in a ~~platinum-catalyzed-cured~~ silicone matrix. **It has been evaluated in 5 completed clinical trials.**⁵

The first clinical trial, IPM 024 was conducted in Belgium, enrolled 16 healthy, HIV-uninfected, sexually abstinent women, between 18 to 40 years of age. The women were randomly assigned to a dapivirine (25 mg) matrix ring or a placebo ring for 28 consecutive days. No SAEs were reported in the dapivirine VR group. No AEs were judged by the investigator to be related to the study agent. Most dapivirine VR group participants, 87.5% (7/8), experienced at least one TEAE. Of the women in the dapivirine VR group who experienced a TEAE, 50% (4/8) reported headache. Of the participants using dapivirine VRs, 50% experienced Grade 1 or Grade 2 metrorrhagia, 38% experienced vulvovaginal discomfort and 25% experienced nasopharyngitis. One participant experienced a Grade 1 vaginal hemorrhage in the dapivirine VR group.

IPM 013 was a Phase I, randomized, double-blind, placebo-controlled trial conducted over 3 months at one research center in Belgium (IPM 013).⁵ Forty-eight healthy, HIV-negative, sexually active women, 18 to 40 years of age, were assigned in groups of eight to one of two groups, Group A or Group B (unblinded assignment). Within each group, participants were randomized in a blinded manner, in a 3:1 ratio, to either the dapivirine ring or placebo ring, for a total of four treatment arms. In Group A, the first vaginal ring was removed on Day 28, and a second vaginal ring inserted after 3 days, on Day 31, for another 28 days. In Group B, the first vaginal ring was removed on Day 35, and a second vaginal ring was inserted after 3 days, on Day 38, for another 21 days. A third vaginal ring was inserted immediately following removal of the second ring on

Day 59, and was worn for 24 hours. No SAEs were reported during the trial. One participant discontinued the trial due to a TEAE of generalized pruritus; the event was not considered serious, of Grade 2 (moderate) intensity, and regarded by the investigator as possibly related to use of the dapivirine ring. No TEAEs were assessed by the investigator as definitely or probably related to the dapivirine ring, and a similar percentage of participants in the dapivirine and placebo ring groups had TEAEs considered to be possibly related to the vaginal ring.

IPM 015, ~~was~~ a double-blind, randomized, placebo- controlled Phase 1/2 trial **conducted at 10 research centers in Kenya, Malawi, Tanzania and South Africa.** The trial was performed in 280 healthy, HIV-negative women, ~~followed women who inserted a vaginal ring once every 21-3524-32~~ days over a 12-week period. Five ~~serious~~ SAEs **occurred during the trial, of which four occurred in placebo participants.**¹¹ ~~were reported, one occurring in the dapivirine ring arm.~~¹⁷ None of the SAEs were judged to be related to product. No TEAEs led to premature discontinuation of ring use.

~~IPM 015 was designed to assess and compare the safety of a dapivirine vaginal ring against a placebo vaginal ring when inserted once every 28 days over a 12-week period among healthy, HIV-negative women. Five SAEs occurred during the trial, of which four occurred in placebo participants. One participant in the dapivirine treatment group reported Grade 3 tonsillitis, which was unrelated to the investigational product. Four participants in the placebo treatment group reported one instance each of bronchiectasis (Grade 3), peritonsillar abscess (Grade 3), suicide attempt (Grade 3), and hemopneumothorax (Grade 4). The hemopneumothorax was caused by a physical assault; this event was unrelated to the investigational product. A chemical pregnancy was reported for one participant in the placebo ring group who discontinued product use, but continued to attend the research center for safety evaluations and completed the remainder of trial visits. In IPM 015, two vaginal hemorrhage bleeding events were reported; both occurred in the placebo ring arm. Apart from the latter two events, chemical pregnancy and hemopneumothorax, none of the SAEs or TEAEs led to premature discontinuation of ring use.~~

~~At least one TEAE was experienced by most participants (81% in the dapivirine ring group, and 86% in the placebo ring group). Metrorrhagia was reported most frequently reported, with a similar incidence observed in the dapivirine ring and placebo ring groups.~~

~~At least 10% of participants using dapivirine rings experienced the following TEAEs: gynecological chlamydia infection, urinary tract infection, vaginal candidiasis, and upper respiratory tract infection. Participants in both the dapivirine and placebo ring treatment groups experienced gynecological chlamydia infection at a rate of 16% (22/140). Urinary tract infection was experienced by participants using dapivirine and placebo rings, 13% (18/140) and 10% (14/140), respectively.~~

~~Approximately 38% (54/140) of participants in the dapivirine ring group and 42% (59/140) of participants in the placebo ring group reported Grade 1 (mild) TEAEs. Forty-one percent (57/140) of participants in the dapivirine ring group and 37% (52/140) of participants in the placebo ring group experienced Grade 2 (moderate) events.~~

~~Grade 3 (severe) TEAEs were experienced by three participants in the dapivirine ring group: tonsillitis (also reported as an SAE), vulvovaginal pruritus (considered possibly related), and increased ALT level. Nine participants in the placebo ring group experienced Grade 3 AEs: bronchiectasis (SAE), peritonsillar abscess (SAE), metrorrhagia, decreased blood phosphorus (two participants), decreased lymphocyte count, neutropenia (considered possibly related), stress, and a suicide attempt (SAE).~~

~~One Grade 4 (potentially life-threatening) TEAE occurred in the placebo treatment group: one participant died due to hemopneumothorax, which occurred as a result of physical assault.~~

~~No TEAEs were considered by the Investigator as definitely related to ring use during IPM 015. The~~

most commonly observed TEAE that was regarded as possibly or probably related to ring use was metrorrhagia, which was reported for 6% (9/140) of participants using dapivirine rings and 3% (4/140) of participants using placebo rings.

~~IPM 024, conducted in Belgium, enrolled 16 healthy, HIV-uninfected, sexually abstinent women, between 18 to 40 years of age. The women were randomly assigned to a dapivirine (25 mg) ring or a placebo ring for 28 consecutive days. No SAEs were reported in the dapivirine VR group. No AEs were judged by the investigator to be related to the study agent. Approximately 88% of participants in the dapivirine ring group, and 100% in the placebo ring group had at least one TEAE. No events were assessed by the investigator as possibly, probably or definitely related to the dapivirine or placebo ring.~~

IPM 028, the fourth trial of Ring-004 was a Phase I open-label, randomized, 3-period, 2-sequence, cross-over trial, to assess the drug-drug-interaction potential between Ring-004 and miconazole nitrate, administered as a single dose (1200 mg) vaginal capsule (Gyno-Daktarin®) in HIV-negative women, 18 to 40 years of age.⁵ The trial was conducted at a Phase I unit in Belgium and enrolled 36 women, randomly assigned to one of two treatment sequences, ABC or BAC, during which they received three treatments, each separated by a washout period of 3 weeks: Treatment A = Dapivirine Vaginal Ring-004 inserted for 28 days; Treatment B = Dapivirine Vaginal Ring-004 inserted for 28 days along with a single dose of miconazole nitrate on Day 0; Treatment C = a single dose of miconazole nitrate inserted on Day 0. One SAE (fracture of the right acetabulum) was reported in a participant during the washout period who had been assigned to initial treatment with the dapivirine ring and miconazole vaginal capsule (Treatment B). The event was assessed as severe (Grade 3) and regarded by the Investigator as unrelated to the IP. One TEAE was considered by the Investigator as related to IP use during the trial. The participant was enrolled in Treatment Sequence ABC and experienced moderate (Grade 2) vulvovaginal candidiasis during the ring use period of Treatment A, two days before the scheduled ring removal. Based on all safety evaluations performed, no overall clinically significant differences were observed between treatment with the dapivirine vaginal ring alone, in co-administration with miconazole, or miconazole alone.

IPM 034, the fifth trial of Ring-004 was a Phase I open-label, parallel group trial, to assess the release profile of Ring-004 over extended periods of ring use in HIV-negative women, 18 to 40 years of age. The trial was conducted at a Phase I unit in Belgium and enrolled 40 women in five groups (Groups A, B, C, D and E) of eight women each. Each woman was administered with one dapivirine ring and instructed to wear the ring continuously for a period of 7, 14, 28, 56, or 84 days (1, 2, 4, 8, or 12 weeks). One SAE (thoracic vertebral fractures following a motor vehicle accident) was reported in a participant using the dapivirine ring in Group C. The event was assessed as severe (Grade 3) and regarded by the Investigator as unrelated to the IP. Product-related TEAEs were reported for four women during the trial of whom three experienced mild vaginal discharge (one woman with a 56-day ring use period and two women with an 84-day ring use period) and one experienced moderate bacterial vaginitis (84-day ring use period). Based on all safety evaluations performed during the trial, no overall clinically significant differences were observed between the different ring use periods.

14. *Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, Safety, safety data for study MTN-013/IPM 026 was updated:*

~~MTN-013/IPM 026, a Phase 1 safety and pharmacokinetics study of dapivirine VR, maraviroc VR, dapivirine/maraviroc VR and placebo VR enrolled **approximately** 48 women between the ages of 18-40. The participants were randomized in a 1:1:1:1 ratio to 28 days of continuous study vaginal ring use. Over the course of 52 days, 14 follow-up visits occurred. Safety and intensive PK assessments were conducted on all participants. Safety comparisons of each product to placebo as well as data related to absorption and distribution is anticipated to be available in the third quarter of 2013. **There was no**~~

statistically significant difference in the number of participants with genitourinary AEs between placebo arm and any other treatment arms. Twenty-two women experienced 33 grade 1 and one grade 2 related genitourinary AEs.¹² Two grade 2 AEs were determined to be related to study product. At Day 28, dapivirine vaginal fluid levels were 14.9 µg/mL in women assigned to the dapivirine only ring.

15. Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, Safety, safety data for study IPM 027 was updated to reflect the new Investigator's Brochure:

In March of 2012, **IPM 027, also known as The Ring Study, also known as IPM 027**, was initiated... The study is being conducted at several sites in sub-Saharan **South Africa and Uganda**... The study is anticipated to conclude in 2015/16.

16. Section 2.6.1, CLINICAL STUDIES OF DAPIVIRINE VAGINAL RINGS, Safety, safety data for study MTN-020 was updated:

MTN-020, A Study to Prevent Infection with a Ring for Extended Use ~~or~~ (ASPIRE), is a Phase 3 clinical trial designed to assess the ~~effectiveness~~**efficacy** and safety of a ring containing ~~contain~~ 25 mg of dapivirine, for the prevention of HIV-1 acquisition in women. The double-blind, randomized controlled trial is being conducted in HIV-uninfected women, between the ages 18 – 45., ~~in multiple sites across sub-Saharan Africa.~~ In August of 2012, ASPIRE initiated the enrollment of 3476 participants. **A total of 2629 women from Malawi, South Africa, Uganda, and Zimbabwe have enrolled in the trial. Participants replace the ring monthly for a minimum of one year. MTN-020 aims to determine the safety and efficacy of the dapivirine ring in preventing HIV-1 infection among health sexually active HIV-uninfected women when inserted vaginally once every 4 weeks. Additional goals of MTN-020 include the assessment of participant acceptability and adherence to the investigational product, HIV-1 drug resistance mutations among participants who acquire HIV-1 infection and establishing steady state drug concentrations in the study population.** The study is anticipated to conclude in 2015.

17. Section 3.1, PRIMARY OBJECTIVE, edit was made to lengthen the study duration:

Safety

To assess the safety of dapivirine (25 mg) administered via a silicone vaginal ring in HIV-uninfected adolescent females, when inserted once every 4 weeks during ~~4224~~ weeks of study product use

18. Section 3.2, SECONDARY OBJECTIVES, edits were made to lengthen the study duration:

Acceptability

To evaluate the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a ~~4224~~ week period

Adherence

To evaluate the adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a ~~4224~~ week period

19. Section 3.3, EXPLORATORY OBJECTIVES, edit was made to lengthen the study duration:

Vaginal Microenvironment

Describe the genital microenvironment over ~~4224~~ weeks of study product use

20. Section 4.1, *IDENTIFICATION OF STUDY DESIGN*, edit was made to lengthen the study duration:

MTN-023/IPM 030 is a Phase 2a, two-arm, placebo-controlled, double-blinded, multi-site, randomized trial of dapivirine VR versus placebo VR (a vaginal ring inserted once every 4 weeks for a total of approximately ~~42~~4 weeks) in sexually experienced, HIV-uninfected adolescent females.

21. Section 4.4, *TIME TO COMPLETE ACCRUAL*, edit was made to lengthen the study duration:

Accrual is expected to be complete in approximately ~~6-9~~12 months at each site.

22. Section 4.6, *EXPECTED DURATION OF PARTICIPATION*, edit was made to lengthen the study duration:

The expected trial duration for participants is approximately ~~43~~25 weeks.

23. Section 5.2, *INCLUSION CRITERIA*, a minor clarification was made to Inclusion #10:

Per participant report at Screening, history of ~~penile-vaginal~~sexual intercourse (at least one episode in participant's lifetime)

24. Section 5.3, *EXCLUSION CRITERIA*, a minor edit was made for consistency with other text in the section:

Note: Otherwise eligible participants diagnosed with UTI/RTI during Screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved.

25. Section 6.4.2, *STUDY PRODUCT DISPENSING*, edit was made to lengthen the study duration:

Dispensing takes place on the day of Enrollment, and at the ~~4-Week and 8-Week~~monthly follow-up visits **until the final clinic visit**.

26. Section 6.4.4, *RETRIEVAL OF STUDY PRODUCT*, edit was made to lengthen the study duration:

For each participant, all VRs remaining in the participant's possession must be retrieved at the ~~42~~24-Week (Final Clinic) Visit.

27. Section 6.6, *CONCOMITANT MEDICATIONS*, edits were made to the first paragraph, second sentence:

All concomitant medications ~~as well as illicit substances~~ reported throughout the course of the study will be recorded on case report forms designated for that purpose.

28. Section 6.7, *USE OF INTRAVAGINAL MEDICATIONS/PRODUCTS AND PRACTICES*, edits were made to clarify instructions on use of intravaginal products prior to visits and for grammatical clarity:

Please note, neither the use of tampons or sex toys, nor participant engagement in coitus is restricted, however, participants will be instructed to abstain from **these practices and from inserting anything into the vagina** any non-study vaginal products for 72 hours prior to each **monthly** follow-up visit, including abstaining from penile-vaginal intercourse. Participant report of sexual intercourse in the past 72 hours will be assessed at each follow-up visit where samples are **to** be collected for PK.

29. Section 7, *STUDY PROCEDURES*, Figure 2 was reformatted for clarity:

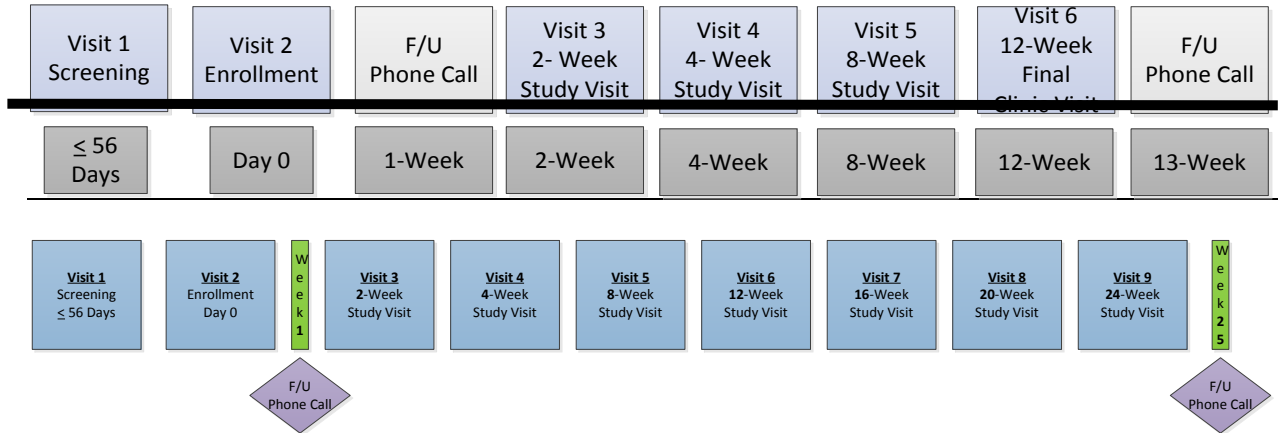


Figure 1: Study Visit Schedule

30. Section 7.2, SCREENING VISIT, Table 5: Screening Visit, edits were made to clarify which tests to perform at sites with capacity to do them:

Urine: Nucleic acid amplification test (NAAT) for *Neisseria gonorrhoeae* and *Chlamydia trachomatis* (GC/CT), **at sites with capacity**

Pelvic: Vaginal swab for rapid Trichomonas test, **at sites with capacity**

Pelvic: **Vaginal swab for Trichomonas/GC/CT[‡], [‡] At sites using Aptima only**

31. Section 7.3, ENROLLMENT VISIT (Day 0): edits were made to clarify which tests to perform at sites with capacity to do them:

Urine: NAAT for GC/CT **at sites with capacity**

Pelvic: Vaginal swab for rapid Trichomonas test, **at sites with capacity**

Pelvic: **Vaginal swab for Trichomonas/GC/CT[‡], [‡] At sites using Aptima only**

32. Section 7.4.1, VISIT 3: 2-WEEK STUDY VISIT, Table 7: 2-Week Study Visit, Product Adherence Counseling was changed from required to if indicated:

Product adherence*

33. Section 7.4.1, VISIT 3: 2-WEEK STUDY VISIT, Table 7: Urine, Pelvic & Footnote sections were edited to clarify which tests to perform at sites with capacity to do them:

Urine: NAAT for GC/CT, **at sites with capacity**

Pelvic: Vaginal swab for rapid Trichomonas test, **at sites with capacity***

Vaginal swab for Trichomonas/GC/CT[‡]

[‡] At sites using Aptima only

34. Section 7.4.1, VISIT 3: 2-WEEK STUDY VISIT, Table 7: Vaginal fluid for PK was added:

Vaginal fluid for PK

35. Section 7.4.1, VISIT 3: 2-WEEK STUDY VISIT, Table 7: If needed collection of used VR was added:

Collection of used study VR*

36. Section 7.4.2, VISIT 4: 4-WEEK STUDY VISIT, Table 8: 4-Week Study Visit, Urine, Pelvic & Footnote sections were edited to clarify which tests to perform at sites with capacity to do them:

Urine: NAAT for GC/CT, **at sites with capacity***

Pelvic: Vaginal swab for rapid Trichomonas test, **at sites with capacity***

Vaginal swab for Trichomonas/GC/CT*◆

‡ At sites using Aptima only

37. Section 7.4.2, VISIT 4: 4-WEEK STUDY VISIT, Table 8: 4-Week Study Visit, CVL for Biomarkers was moved.

38. Section 7.4.3, VISIT 5: 8-WEEK STUDY VISIT, Table 9: 8-Week Study Visit, Perform Pelvic Examination was changed from required to if indicated:

Perform pelvic examination*

39. Section 7.4.3, VISIT 5: 8-WEEK STUDY VISIT, Table 9: 8-Week Study Visit, Blood, PK sample was deleted:

Collect blood for:

○ PK

40. Section 7.4.3, VISIT 5: 8-WEEK STUDY VISIT, Table 9: 8-Week Study Visit, Laboratory and Study Product Supply sections were updated to reflect longer study duration and some procedure wording was slightly adjusted to clarify which tests to perform at sites with capacity to do them:

- Collect pelvic samples
 - ~~Vaginal~~ Vaginal pH*
 - Saline wet mount for BV*
 - KOH wet mount for candidiasis*
 - Vaginal swab for rapid Trichomonas test, **at sites with capacity***
 - **Vaginal swab for Trichomonas/GC/CT*◆**
 - Herpes lesion testing*

- Collect urine for:
 - hCG
 - NAAT for GC/CT*
 - , at sites with capacity*
 - Dipstick UA and/or urine culture, per local standard of care*

41. Section 7.4.4, 12-WEEK STUDY VISIT, Table 10, Procedures were adjusted to reflect longer study duration and some procedure wording was slightly adjusted for clarity:

7.4.4 Visit 6: 12-Week Final Clinic Study Visit/ ~~Early Termination Visit~~

Table 10: 12-Week ~~Final Clinic Visit/ Early Termination Study Visit~~

12-Week Study Visit		
Component	Procedures	
Administrative and Regulatory	<ul style="list-style-type: none"> ● Review/update locator information ● Provide reimbursement ● Schedule next contact study visit 	
Behavioral/Counseling	<ul style="list-style-type: none"> ● Administer behavioral assessment(s) –Adherence & Acceptability ● Provide counseling <ul style="list-style-type: none"> ○ HIV pre-and post-test ○ HIV/STI risk reduction ○ Protocol adherence ○ Product adherence ○ HIV pre-and post-test* ○ Male condom* ○ Administer In-depth Interview (subset of participants only) 	
Clinical	<ul style="list-style-type: none"> ● Review/update medical history ● Review/update menstrual history ● Review/update concomitant medications ● Perform targeted physical examination ● Perform pelvic examination <ul style="list-style-type: none"> ○ Including an assessment of cervical ectopy ● Record/update AEs ● Provide contraceptive counseling ● Disclosure of available test results ● Treat for UTIs/RTIs/STIs or refer* 	
Laboratory	Urine	<ul style="list-style-type: none"> ● Collect urine for: <ul style="list-style-type: none"> ○ hCG ○ NAAT for GC/CT, at sites with capacity* ○ Dipstick UA and/or urine culture, per local standard of care*
	Blood	<ul style="list-style-type: none"> ● Collect blood for: <ul style="list-style-type: none"> ○ PK ○ HIV-1 serology (confirmatory tests as needed) ○ Serum chemistries* ○ CBC with platelets* ○ Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	<ul style="list-style-type: none"> ● Collect pelvic samples <ul style="list-style-type: none"> ○ CVL for biomarkers ○ Vaginal fluid for PK ○ Vaginal swab for Gram stain ○ Vaginal swab for quantitative vaginal culture ○ Vaginal swab for biomarkers ○ Vaginal pH ○ Saline wet mount for BV* ○ KOH wet mount for candidiasis* ○ Vaginal swab for rapid Trichomonas test, at sites with capacity* ○ Vaginal swab for Trichomonas/GC/CT*♦ ○ Herpes lesion testing*

Table 10: 12-Week Final Clinic Visit/ Early Termination Study Visit

12-Week Study Visit	
Component	Procedures
Study Product Supply	<ul style="list-style-type: none"> ● Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR <i>Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist</i> ● Collection of used study VR ● Clinician directed digit exam to check vaginal ring placement* ● Provision of male condoms*

42. Section 7.4.4, VISIT 7 AND VISIT 8: 16-WEEK AND 20-WEEK STUDY VISITS, Table 11, This table is new and reflects longer study duration; and some procedure wording was slightly adjusted for clarity:

7.4.4 Visit 7 and Visit 8: 16-Week and 20-Week Study Visits

16-Week and 20-Week Study Visits		
Component	Procedures	
Administrative and Regulatory	<ul style="list-style-type: none"> ● Review/update locator information ● Provide reimbursement ● Schedule next contact 	
Behavioral/Counseling	<ul style="list-style-type: none"> ● Administer behavioral assessment(s) - Adherence ● Provide counseling <ul style="list-style-type: none"> ○ Protocol adherence ○ Product adherence ○ HIV/STI risk reduction ○ HIV pre-and post-test* ○ Male condom* 	
Clinical	<ul style="list-style-type: none"> ● Review/update medical history ● Review/update menstrual history ● Review/update concomitant medications ● Perform targeted physical examination ● Perform pelvic examination* ● Record/update AEs ● Disclosure of available test results ● Provide contraceptive counseling ● Treat for UTIs/RTIs/STIs or refer* 	
Laboratory	Urine	<ul style="list-style-type: none"> ● Collect urine for: <ul style="list-style-type: none"> ○ hCG ○ NAAT for GC/CT, at sites with capacity* ○ Dipstick UA and/or urine culture, per local standard of care*
	Blood	<ul style="list-style-type: none"> ● Collect blood for: <ul style="list-style-type: none"> ○ HIV-1 serology (confirmatory tests as needed)* ○ Serum chemistries* ○ CBC with platelets* ○ Syphilis serology (confirmatory tests as needed)*
	Pelvic Samples	<ul style="list-style-type: none"> ● Collect pelvic samples <ul style="list-style-type: none"> ○ Vaginal pH* ○ Vaginal swab for rapid Trichomonas test, at sites with capacity* ○ Vaginal swab for Trichomonas/GC/CT*♦ ○ Saline wet mount for BV* ○ KOH wet mount for candidiasis* ○ Herpes lesion testing*

Study Product Supply	<ul style="list-style-type: none"> ● Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR Note: If the participant is not able to self-insert the study VR, the clinician/designee may assist ● Clinician directed digit exam to check vaginal ring placement* ● Collection of used study VR ● Provision of male condoms *
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43. Section 7.4.5, 24-WEEK FINAL CLINIC VISIT/EARLY TERMINATION VISIT, Table 10, This table is new and reflects longer study duration; and some procedure wording was slightly adjusted for clarity and clarify which tests to perform at sites with capacity to do them:

7.4.5 Visit 9: 24-Week Final Clinic Visit/ Early Termination Visit

24-Week Final Clinic Visit/ Early Termination Visit		
Component	Procedures	
Administrative and Regulatory	<ul style="list-style-type: none"> ● Review/update locator information ● Provide reimbursement ● Schedule next contact 	
Behavioral/Counseling	<ul style="list-style-type: none"> ● Administer behavioral assessment(s) –Adherence & Acceptability ● Provide counseling <ul style="list-style-type: none"> ○ HIV pre-and post-test ○ HIV/STI risk reduction ○ Male condom* ● Administer In-depth Interview (subset of participants only) 	
Clinical	<ul style="list-style-type: none"> ● Review/update medical history ● Review/update menstrual history ● Review/update concomitant medications ● Perform targeted physical examination ● Perform pelvic examination <ul style="list-style-type: none"> ○ Including an assessment of cervical ectopy ● Record/update AEs ● Provide contraceptive counseling ● Disclosure of available test results ● Treat for UTIs/RTIs/STIs or refer* 	
Laboratory	Urine	<ul style="list-style-type: none"> ● Collect urine for: <ul style="list-style-type: none"> ○ hCG ○ NAAT for GC/CT-, at sites with capacity ○ Dipstick UA and/or urine culture, per local standard of care*
	Blood	<ul style="list-style-type: none"> ● Collect blood for: <ul style="list-style-type: none"> ○ HIV-1 serology (confirmatory tests as needed) ○ PK ○ Serum chemistries ○ CBC with platelets ○ Syphilis serology (confirmatory tests as needed)*

	Pelvic Samples	<ul style="list-style-type: none"> ● Collect pelvic samples <ul style="list-style-type: none"> ○ Vaginal fluid for PK ○ Vaginal swab for Gram stain ○ Vaginal swab for quantitative vaginal culture ○ Vaginal swab for biomarkers ○ Vaginal swab for rapid Trichomonas test, at sites with capacity ○ Vaginal swab for Trichomonas/GC/CT♦ ○ Vaginal pH ○ CVL for biomarkers ○ Saline wet mount for BV* ○ KOH wet mount for candidiasis* ○ Herpes lesion testing*
Study Product Supply		<ul style="list-style-type: none"> ● Collection of used study VR ● Provision of male condoms*

44. Section 7.4.6, FOLLOW-UP PHONE CALLS: 1-WEEK AND 25-WEEK STUDY TERMINATION, edits were made to lengthen the study duration and clarify some procedures may be done in person:

7.4.6 Follow-Up Phone Calls: 1-Week and 25-Week Study Termination

Study staff will follow-up with participants via phone call one week following the Enrollment Visit and one week following the 25-Week Final Clinic Visit/Early Termination Visit. Study staff will inquire about AEs the participant may have experienced as a result of the study product or procedures performed during the Enrollment Visit or the 25-Week Final Clinic Visit/Early Termination Visit.

Table 10: 1-Week and 25-Week Study Termination Follow-Up Phone Calls*

Component	Procedures
Administrative and Regulatory	<ul style="list-style-type: none"> ● Reimbursement~
Clinical	<ul style="list-style-type: none"> ● Record/update AEs ● Concomitant medications

~ Sites to reference SOPs *Visit procedures may be conducted in-person, see SSP for additional details

45. Section 7.5, FOLLOW-UP PROCEDURES FOR PARTICIPANTS WHO DISCONTINUE STUDY PRODUCT, minor wording edit was made:

Please note, in the event a participant permanently or temporarily discontinues study product, regardless of reason, behavioral assessments/evaluations will be administered according to guidance from the protocol team.

46. Section 7.5.2, PARTICIPANTS WHO BECOME PREGNANT, edits were made to lengthen the study duration and to offer participants the opportunity to enroll in protocol MTN-016 should they become pregnant while enrolled in MTN-023:

Pregnancy outcomes will be reported on relevant CRFs for participants found to be pregnant at the 25-Week Final Clinic Visit/Early Termination Visit.

Participants who become pregnant while on study product may be offered enrollment in MTN-016 (www.mtnstopshiv.org), provided their study site is taking part in MTN-016.

47. Section 7.7, PHARMACOKINETICS, edits were made to lengthen the study duration & for clarity:

The entire MTN-023/IPM 030 cohort will **be asked to** provide plasma **and vaginal fluid** for PK at the 2-Week, 4-Week, 8-Week and 12-Week study visits. All participants will be asked to provide vaginal fluid

at the ~~4-Week, 8-Week,~~ and ~~12~~**24**-Week study visits.

48. Section 7.7, PHARMACOKINETICS, Table 12, edits made for clarity & to lengthen the study duration:

Visit	Specimens Collected for PK
Visit 3: -2-Week	<input type="checkbox"/> Plasma <input type="checkbox"/> Vaginal fluid
Visit 4: 4-Week	<input type="checkbox"/> Plasma <input type="checkbox"/> Vaginal fluid
Visit 5: 8: 12-Week	<input type="checkbox"/> Plasma <input type="checkbox"/> Vaginal fluid
Visit 6: 12: 24-Week	<input type="checkbox"/> Plasma <input type="checkbox"/> Vaginal fluid

49. Section 7.8, BEHAVIORAL EVALUATIONS AND COUNSELING, edits were made to lengthen the study duration & change the study N:

Adherence will be measured at all monthly visits, including the ~~12~~**24**-Week Final Clinic Visit/Early Termination Visit, via questions about the duration that the ring was out of the vagina and reasons for expulsion and removal.

Acceptability will be measured at the **Enrollment**, ~~12-Week Final Clinic Visit/Early Termination Visit~~ and **24-Week Visits**, via questions about discomfort due to the VR, feeling the VR during daily activity and sex, ease of insertion and removal, partner awareness of VR during sex, and self and partner attitudes towards the VR.

These behaviors will be measured at all ~~scheduled~~ monthly visits, including at the ~~12~~**24**-Week Final Clinic Visit/Early Termination Visit.

In-Depth Interviews:

Approximately ~~40~~6 participants per site will be randomized to complete an in-depth qualitative interview that addresses use of study product during the trial.

The interview will take approximately one hour in duration and will be conducted at the 24-Week Final Clinic Visit/Early Termination Visit.

50. Section 7.10, LABORATORY EVALUATIONS, edits were made to clarify which tests to perform at sites with capacity to do them & reflect renaming of Lab Center:

Urine NAAT for GC/CT, **at sites with capacity**

Rapid Trichomonas test, **at sites with capacity**

Vaginal swab for Trichomonas/GC/CT at sites planning to use the Aptima only

Network Laboratory (NL) **Center (LC)**

51. Section 7.11, SPECIMEN COLLECTION AND PROCESSING, the standard language has changed:

Each study site will adhere to the standards of good clinical laboratory practice in accordance with

current DAIDS Laboratory Requirements, the MTN Laboratory Center Manual (www.mtnstopshiv.org), **and** the MTN-023/IPM 030 Study Specific Procedures Manual (www.mtnstopshiv.org), **and site standard operating procedures** for proper collection, processing, labeling, transport, and storage of specimens at the local laboratory. Specimen collection, testing, and storage at the site laboratories will be documented when applicable using the Laboratory Data Management System (LDMS).

52. *Section 8.4.4, EXPEDITED AE REPORTING PERIOD, edit was made to lengthen the study duration:*

The expedited AE reporting period for this study begins once the participant is randomized and continues up through the participant's ~~13~~**25**-Week Follow-up Phone Assessment/Study Termination

53. *Section 9.8, PREGNANCY, edit was made to offer participants the opportunity to enroll in protocol MTN-016 should they become pregnant while enrolled in MTN-023:*

A participant who becomes pregnant during the course of study participation may be offered participation in MTN-016, HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study, at sites participating in MTN-016. This registry study captures pregnancy outcomes as well as infant health information, (including growth), to evaluate the safety and teratogenic risks of microbicide and oral PrEP exposure in pregnancy. In the event that a study site is not taking part in MTN-016, participants may be contacted to collect pregnancy outcomes.

54. *Section 10.1, OVERVIEW AND SUMMARY OF DESIGN, edit was made to lengthen the study duration:*

This is a multi-site, double-blinded, two arm, 3:1 randomized, placebo-controlled trial to assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal ring, when inserted once every 4 weeks during ~~42~~**24** weeks of study product use by healthy, HIV-uninfected, sexually experienced, adolescent females, 15 - 17 years old (inclusive), as compared with a placebo VR.

55. *Section 10.2, STUDY ENDPOINTS, edits were made to lengthen the study duration:*

Consistent with the primary study objective to assess the safety of dapivirine (25 mg) administered in a silicone elastomer vaginal ring, when inserted once every 4 weeks during ~~42~~**24** weeks of study product use by healthy, HIV-uninfected, sexually experienced, adolescent females, 15 - 17 years old (inclusive), as compared with a placebo, the primary safety endpoints are the proportion of females in each of the two arms with:

Consistent with the secondary study objective to evaluate the acceptability of the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a ~~42~~**24** week period, the following endpoint will be assessed:

To evaluate adherence to the study VR (dapivirine or placebo) in HIV uninfected adolescent females, when inserted once every 4 weeks for a ~~42~~**24** week period the following endpoints will be assessed:

56. *Section 10.4.2, SECONDARY ENDPOINTS, edits were made to lengthen the study duration:*

Acceptability of the study VR (dapivirine or placebo) in sexually experienced, HIV-negative adolescent females for ~~42~~**24** weeks will be determined by participants rating several components of acceptability (e.g., discreetness, likes and dislikes concerning the ring, attitude toward product characteristics, comfort and ease of use, partner reactions, and effect on sex) on a combination of categorical and continuous scales.

Adherence will be measured by the percentage of women who keep the VR inserted at all times in the vagina over the course of ~~42~~**24** weeks.

The PK endpoint is a description of the end of period (28 day post ring insertion) plasma and vaginal fluid dapivirine concentrations at week 2, 4, 8, 12 and 24, and will be descriptively compared to the same results in a recently studied population of adult women (MTN-013/IPM 026).

57. Section 10.4.2, SECONDARY ENDPOINTS, a plasma & vaginal fluid collection at week 2 was added:

Plasma and vaginal fluid will also be collected at Week 2.

58. Section 10.4.2, SECONDARY ENDPOINTS, text referring to VR removal at Day 28 was removed:

The 28 day assessment in each ring period —just before ring removal—represents near steady-state concentrations in prior dapivirine ring studies.

59. Section 10.4.2, SECONDARY ENDPOINTS, text referencing a subset of participants has been removed:

~~This subset was selected to provide a rich dataset of sampling from the female genital tract and chosen to balance feasible logistical complexity which demands a simpler, more sparse sampling approach with the low likelihood of an important difference between populations.~~

60. Section 10.4.2, SECONDARY ENDPOINTS, minor clarity edit was made:

The variability of drug concentration from the unweighed ~~swabs in this~~**swab** cohort will be compared to the variability in the weighed swab cohort.

61. Section 10.5, PARTICIPANT ACCRUAL, FOLLOW-UP AND RETENTION, edits were made to lengthen the study duration:

Based on previous studies of vaginal products, the accrual of 96 eligible participants will take approximately ~~6-9~~**12** months per site.

Each site will target retention of 95% of enrolled participants over the ~~43~~**25**-Week follow-up period.

62. Section 10.8.3, SECONDARY ANALYSES, edit was made to lengthen the study duration:

These rates will be based on participant's self-report of product use at ~~4, 8, and 12 weeks~~**monthly clinic visits**.

63. Section 10.8.4, MISSING DATA, minor grammar edits made:

A sensitivity analysis to assess the potential impact of the missing data will also be performed. This analysis will include imputing the data under the most extreme scenarios of information missingness, such as assuming everyone missing has an extreme value of the missing variable, as well as less informative imputation approaches.

64. Section 12, CLINICAL SITE MONITORING, MTN CORE renamed to MTN LOC; NL renamed to LC:

The IoR/designee also will allow inspection of all study-related documentation by authorized representatives of the MTN ~~CORE~~**LOC**, SDMC, and ~~NLLC~~, IPM and its contractors; National Institute of Allergy and Infectious Diseases (NIAID), NICHD, FDA, OHRP and local and US regulatory authorities.

65. Section 13, HUMAN SUBJECTS PROTECTIONS, MTN CORE renamed to MTN:

The IoR/designee will permit audits by the NIH, IPM, the FDA, OHRP, MTN CORELOC, IRBs, SDMC, and other local and US regulatory authorities or any of their appointed agents.

66. Section 13.3, STUDY COORDINATION, MTN CORE renamed to MTN LOC; NL renamed to LC:

Standardized study-specific training will be provided to all sites by the MTN CORELOC, SDMC, NLLC and other designated members of the Protocol Team.

67. In Section 13.4.1, Risks, edits are made based upon the Treatment-Emergent Adverse Events with Causal Relationships to Dapivirine Ring-004 as Assessed by the Investigator within the Investigator's Brochure:

The most frequently occurring ~~Based on~~ AEs reported among female participants using the dapivirine ~~VR~~ in previous studies, **dapivirine VRs** may be associated with:

- **Metrorrhagia**
- Vaginal bleeding-discharge
- **Vaginal candidiasis**
- **Bacterial vaginitis**
- ~~Vulvovaginal or genital itching and/or discomfort~~
- Urinary tract infection
- ~~Vaginal or vulvovaginal infection (including vaginal candidiasis)~~
- ~~Vaginal or genital discharge~~
- ~~Erythema~~
- ~~Irregular menses~~

68. Section 13.6, PARTICIPANT CONFIDENTIALITY, some text regarding storage of records was removed:

All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number.

69. Section 13.6, PARTICIPANT CONFIDENTIALITY, MTN CORE renamed to MTN LOC; NL renamed to LC:

Representatives of the MTN CORELOC, SDMC, and/or NLLC

70. Appendix I: SCHEDULE OF STUDY VISITS AND EVALUATIONS, edits were made to lengthen the study duration and to clarify which tests to perform at sites with capacity to do them & reflect renaming of Lab Center:

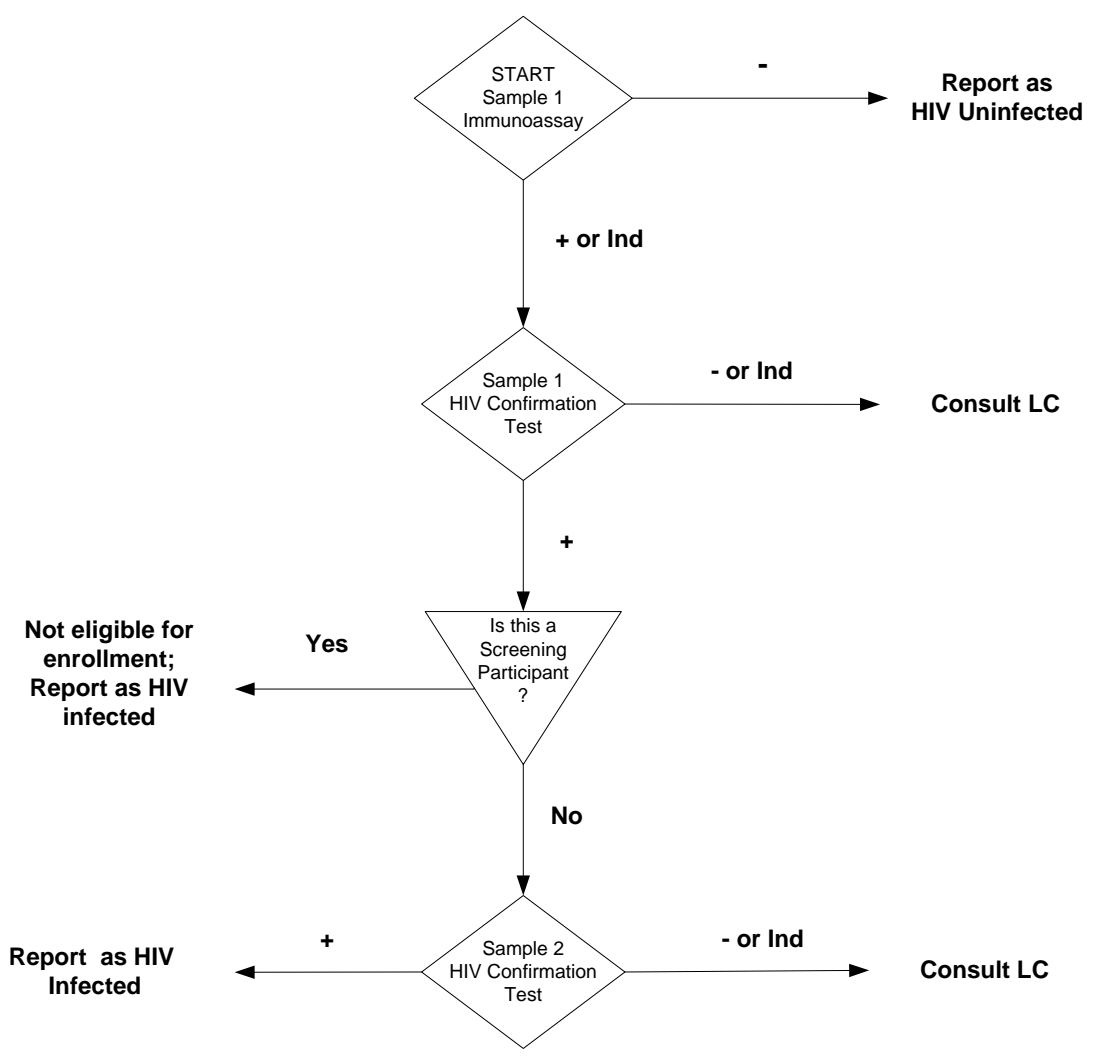
APPENDIX I: SCHEDULE OF STUDY VISITS AND EVALUATIONS

	SCR	ENR	2-Wk Visit	4-Wk Visit	8-Wk Visit	12-Wk Visit	16-Wk Visit	20-Wk Visit	4224-Wk Final Clinic Visit/Early Termination Visit	1-Wk Follow-Up and 4325- Wk Termination Phone Call+
ADMINISTRATIVE AND REGULATORY										
Informed assent and consent(s)	X									
Assign PTID	X									
Locator information	X	X	X	X	X	X	X	X	X	
Demographic information	X									
Eligibility assessment	X									
Eligibility confirmation		X								
Randomization		X								
Provide reimbursement	X	X	X~	X	X	X	X~	X	X	X~
Schedule next visit or contact	*	*	X	X	X	X	X	X	X	
BEHAVIORAL/COUNSELING										

Behavioral evaluation(s)		X		X	X	X	X	X	X	
HIV pre and post-test counseling	X	X	*	*	*	X	X*	*	X	
HIV/STI risk reduction counseling	X	X	X	X	X	X	X	X	X	
Male condom counseling	X	*	*	*	*	*	*	*	*	
Protocol adherence counseling		X	X	X	X	X	X	X		
Product adherence counseling		X	X*	X	X	X	X	X		
In-Depth Interview						▲			▲	
CLINICAL										
Medical history	X	X	X	X	X	X	X	X	X	
Menstrual history	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Full physical examination	X	X								
Tanner assessment	X									
Targeted physical examination			*	X	X	X	X	X	X	
Pelvic examination	X	X	*	X	X*	X	*	*	X	
Assessment of cervical ectopy		X				X			X	
Disclosure of available test results	X	X	X	X	X	X	X	X	X	
Contraceptive counseling	X	X	X	X	X	X	X	X	X	
Record/update AEs			X	X	X	X	X	X	X	X
Treat for UTI/RTI/STIs or refer	*	*	*	*	*	*	*	*	*	
LABORATORY										
Urine hCG	X	X	X	X	X	X	X	X	X	
Urine NAAT for GC/CT, at sites with capacity	X	*	*	*	*	X*	*	*	X	
Dipstick UA and/or urine culture, per local standard of care	*	*	*	*	*	*	*	*	*	
Serum chemistries	X	*	*	*	*	X*	*	*	X	
CBC with platelets	X	*	*	*	*	X*	*	*	X	
HIV-1 serology	X	X	*	*	*	X	*	*	X	
PK- Blood (Plasma)			X	X	X	X			X	
PK-Vaginal fluid			X	X	X	X			X	
Syphilis serology	X	*	*	*	*	*	*	*	*	
Plasma archive		X								
Gram stain		X		X	X	X			X	
Vaginal pH	*	X	*	X	X*	X	*	*	X	
Vaginal swab for quantitative vaginal culture		X		X	X	X			X	
Vaginal swab for biomarkers		X		X		X			X	
CVL for biomarkers		X		X		X			X	
Vaginal swab for Rapid Trichomonas	X	*	*	*	*	X*	*	*	X	
Vaginal swab for Trichomonas/GC/CT	X	*	*	*	*	*	*	*	X	
Saline wet mount for BV	*	*	*	*	*	*	*	*	*	
KOH wet mount for candidiasis	*	*	*	*	*	*	*	*	*	
Herpes lesion testing	*	*	*	*	*	*	*	*	*	
STUDY PRODUCT										
Participants will receive study VR, study VR use instructions and will be instructed to self-insert the study VR		X		X	X	X	X	X		
Clinician directed digit exam to check vaginal ring placement		X		*	*	*	*	*		
Collect study product			*	X	X	X	X	X	X	
Provision of condoms	*	*	*	*	*	*	*	*	*	

X = required, * = if indicated/needed, X~ = sites to reference SOPs, ▲ = Subset of participants only
, + = Visit procedures may be conducted in-person

71. Appendix II, ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING, ENROLLMENT, AND FOLLOW-UP, title was changed, and algorithm revised:
ALGORITHM FOR HIV ANTIBODY TESTING FOR SCREENING, **ENROLLMENT**, AND FOLLOW-UP



Ind: Indeterminate test results
 LC: Laboratory Center

72. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, Who will be in this research study?, edits were made to drop requirement for sexual experience among adolescent enrollees:

Healthy teenage girls who have had sex (vaginal intercourse) at least once and who are found to be eligible will be enrolled in the study.

73. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What will I be asked to do if I join this research study?, edits were made to lengthen the study duration and for clarity:

In this study you will have to wear a vaginal ring for ~~42~~**24** weeks, replacing the vaginal ring every 4 weeks. You will also be asked to come to the clinic for ~~69~~ study visits (including the visit today). If you agree to join this study and your parent/guardian provides their permission, you will be in the study for about ~~13~~**25** weeks.

There will be more teenage girls (**approximately 72 girls**) in the group using the vaginal ring with study product in it than in the group (**approximately 24 girls**) using the placebo vaginal ring.

74. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Screening Procedures, Text added to clarify that Sites are to modify the following section as required by local regulatory authorities to include the specific timing of procedures:

Screening Procedures – [Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures]

75. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Screening Procedures, minor grammar edits were made for clarity:

Study staff will ask you where you live and other questions about you, your medical health (including what medications you are taking), menstrual history, and questions to determine if you are eligible to be **in** this study

A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine ~~the~~**your** vagina and the cervix.

76. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Screening Procedures, requirement for sexual experience among adolescent enrollees has been removed:

Not having sex for 72 hours before the study visits-, **if you are currently having sex**

You will be required to use birth control for at least 30 days before you attend your Enrollment Visit-, **even if you are not currently having sex.**

77. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Screening Procedures, clarification was made about use of vaginal products prior to enrollment visit:

Not using the following for the duration of your study participation **and for 5 days prior to enrollment:** spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants not approved for use by this study.

78. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, Text added to clarify that Sites are to modify the following section as required by local regulatory authorities to include the specific timing of procedures:

Enrollment and Follow-up Procedures – [Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures]

79. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, edits were made to lengthen the study duration:

4316-Week Study Visit

20-Week Study Visit

24-Week Study Visit

25-Week Follow-up Phone Call

80. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, minor grammar edit was made:

You will be asked to avoid inserting the following vaginal products and/or objects into your vagina;: spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, **or** lubricants, for the 5 days prior to Enrollment and throughout the duration of study participation.

81. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, references regarding any prior sexual experience. Text was added stating that participants might be asked about sexual history, if applicable:

Ask you questions about your vaginal practices, ~~including sexual activity~~

You may be asked to answer questions that may make you uncomfortable, for example, questions about drug use **or sexual activity**.

82. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, details of the physical exam were deleted:

Perform a physical exam; ~~which will include measuring your height, weight, temperature, pulse, blood pressure, and perform other procedures, as needed at some visits~~

83. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, edits were made to clarify that some procedures do not occur at

each visit and that they are for research purposes:

Perform a physical exam; ~~which will include measuring your height, weight, temperature, pulse, blood pressure, and perform other procedures, as needed~~ **at some visits**

Take a sample of your blood **at some visits**

Check on the health of your blood, liver and kidneys ~~at your final visit.~~ **(these tests may be performed at any visit, if indicated).**

Test your urine **at some visits**

84. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, reference to a speculum exam was removed, and wording regarding pelvic exam, pelvic sample collection, and menstruation was revised for clarity:*

Perform a pelvic examination:

~~The study doctor or nurse will use a speculum for this exam. A speculum is plastic or metal tool used to help open the vagina so that the doctor or nurse can examine the vagina and the cervix. They will~~ **at some visits:**

To check for signs of infection, and other problems.

~~They will~~**To** take some fluids from your vagina using a swab. ~~They~~ **for research purposes only. Staff** will also take some fluids from your cervix using a swab to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary. ~~Some of these swabs may be self-collected. If you are uncomfortable collecting the fluid, a study clinician can collect it for you.~~

~~During these~~ **some** pelvic examination ~~exams,~~ a vaginal wash will be performed.

Talk with study staff about how to properly wear and use the vaginal ring, including information about wearing the vaginal ring during ~~menses~~**your period**, how to clean the vaginal ring if it falls out, etc.

85. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, sentence about dispensing an oral medication to treat STIs/STDs was removed:*

~~If you are found to have an STI, STD or other health issues, you may be asked to use an oral medication rather than a vaginal medication.~~

86. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, clarifies that the exam to check the positioning of the ring only occurs as necessary:*

Have an exam to ensure that the vaginal ring is properly inserted, **if needed**

87. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, sentence about reimbursement for text messages was removed and text regarding payment for text messages was modified (Bullet 2 after study visit schedule):

~~Information will be given to you regarding reimbursement for text messages in a later section.~~

You will be asked to receive and reply to phone calls from the study staff. In addition, you will be asked to answer questions about your study product use by text message on a cell phone. You will be ~~paid~~ **reimbursed** for each text message session. You will receive text message(s) once a week. ~~The~~ **Your** answer(s) will be private.

88. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, sentence about possible infection was edited for clarity:

At any time during the study, the following may need to be collected if you are having symptoms of, **infection** or if clinicians suspect you may have an infection:

89. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, In-depth Interview Subset, subject N was modified:

About ~~406~~ teenage girls from each site will participate in the in-depth interview portion of this study.

90. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, In-depth Interview Subset, text about participants being asked about how the ring affects their interactions with their partner was modified for clarity:

Additionally you will be asked about how your vaginal ring use was affected by your home setting, relationships with your friends and/or ~~sex partner~~ **boyfriend(s), or girlfriends**, and your experience with sex (if you are currently sexually active), ~~and your sex partner's response to your vaginal ring use.~~

91. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, Pregnancy, requirement for sexual experience among adolescent enrollees has been removed:

~~You~~ **Even if you are not currently sexually active, you** must agree to use an effective method of birth control (e.g., birth control pills, hormonal-based methods, intrauterine device (IUD), the patch) but you cannot use a vaginal ring for birth control.

92. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, Risks of Study Drugs, has been updated to reflect the new Investigator's Brochure:

- Vaginal bleeding **at irregular intervals, particularly between your expected menstrual periods**

- ~~Genital area and/or vaginal itching and/or discomfort~~
- ~~Urinary infection~~
- ~~Vaginal or genital area infection (including vaginal fungal infection)~~
- Vaginal or genital discharge
- ~~Erythema (redness of skin)~~
- **Yeast infection**
- **Urinary tract infection**

93. *Appendix III, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Other Possible Risks, edit made for comprehensiveness:*

Finding out your HIV status could also cause problems between you and your partner **or your family**.

94. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, Other Possible Risks, requirement for sexual experience among adolescent enrollees has been removed:*

if you are currently sexually active, ways to protect against HIV and other infections passed through sex, and your test results.

It is also possible for you and/or your partner to feel the vaginal ring during sexual activity-, **if you are currently sexually active**.

95. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, Other Possible Risks, minor edits made for clarity:*

If you are chosen for the in-depth interview subset, study staff **will** talk with you about how and when you used the study products, **and** they will audio record the discussion using a digital audio recorder.

96. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, New Information, text about new data being shared with the participant has been removed:*

Researchers working on this study will provide you with ~~any data or~~ new information about HIV prevention that becomes available, regardless of the product, if it is found to be effective in **adolescent females**.

97. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT, edit has been made for clarification regarding a final visit if subject chooses to discontinue participating in study:*

In the event that you are removed from or choose to leave this study, you will be asked to return your vaginal ring **and to come back for one final clinic visit**.

98. Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, ASSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION, participant & parent/guardian initialing section has been modified in an effort to align more closely with the standard MTN STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION language, also for clarity, to reduce confusion & minor grammar edit was made:

There might be a small amount of urine, blood, vaginal and cervical fluids 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 leftover urine, blood, vaginal and cervical fluids, and related health information for ~~testing~~ **use** in future studies. If you agree, your samples **and related health data** will be stored safely and securely. Only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. There is no time limit on how long your samples will be stored. **The specific type of testing planned for these specimens is not yet known, however samples may be used by the MTN Laboratory Center to complete additional quality assurance and control testing, ensuring that the tests perform correctly and supply accurate data.** Any future studies ~~testing, beyond the quality assurance and control testing,~~ ~~that may be done~~ will also have to be approved by an Ethics Committee/ Institutional Review Board. **No genetic testing (limited or genome-wide) is planned.** You can still enroll in this study if you decide not to have urine, blood, vaginal and cervical fluids stored for future studies. You can withdraw your assent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. **However, researchers will not be able to destroy samples or information from research that is already underway.**

PARTICIPANT INITIALS	
_____ Initials	I DO agree to allow my biological specimens and health data to be stored and used in future research studies.
_____ Date	
_____ Initials	I DO NOT agree to allow my biological specimens and health data to be stored and used in future research studies.
_____ Date	
PARENT/GUARDIAN INITIALS	
_____ Initials	I DO agree to allow my child's biological specimens and health data to be stored and used in future research studies.

Date

Initials

I DO NOT agree to allow my child's biological specimens and health data to be stored and used in future research studies.

Date

99. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Informed Consent, requirement for sexual experience among adolescent enrollees has been removed:*

You may have previously been asked to take part in this research study because you were a female between the ages of 15 and 17 years ~~and have had sex at least once.~~

100. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Informed Consent, text inserted to allow possibility of being reconsented using this form:*

Before you decide if you want to join **(or continue in)** this study, we want you to know about the study.

101. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Who will be in this research study? Requirement for sexual experience among adolescent enrollees has been removed:*

Healthy teenage girls who ~~have had sex (vaginal intercourse) at least once and who~~ are found to be eligible will be enrolled in the study.

102. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What will I be asked to do if I join this research study? edits were made to lengthen the study duration and for clarity:*

In this study you will have to wear a vaginal ring for ~~12~~**24** weeks, replacing the vaginal ring every 4 weeks. You will also be asked to come to the clinic for ~~6~~**9** study visits (including the visit today). If you agree to join this study, you will be in the study for about ~~13~~**25** weeks.

There will be more teenage girls (**approximately 72 girls**) in the group using the vaginal ring with study product in it than in the group (**approximately 24 girls**) using the placebo vaginal ring.

103. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Screening Procedures, Text added to clarify that Sites are to modify the following section as required by local regulatory authorities to include the specific timing of procedures:*

Screening Procedures – [Sites to modify the following section as required by local regulatory

authorities to include the specific timing of procedures]

104. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Screening Procedures, Requirement for sexual experience among adolescent enrollees has been removed:*

Not having sex for 72 hours before the study visits, **if you are currently having sex**

Not using the following for the duration of your study participation **and for 5 days prior to enrollment:** spermicides, diaphragms, contraceptive vaginal rings, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants not approved for use by this study.

You will be required to use birth control for at least 30 days before you attend your Enrollment Visit, **even if you are not currently having sex.**

105. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, Text added to clarify that Sites are to modify the following section as required by local regulatory authorities to include the specific timing of procedures:*

Enrollment and Follow-up Procedures – [Sites to modify the following section as required by local regulatory authorities to include the specific timing of procedures]

106. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, edits were made to lengthen the study duration and text elsewhere in this section has been modified for clarity and consistency:*

16-Week Study Visit

20-Week Study Visit

24-Week Study Visit

25-Week Follow-up Phone Call

You will be asked to receive and reply to phone calls from the study staff. In addition, you will be asked to answer questions about your study product use by text message on a cell phone. You will be ~~paid~~ **reimbursed** for each text message session. You will receive text message(s) once a week. Your answer(s) will be private.

Check on the health of your blood, liver and kidneys ~~at your final visit~~ **(these tests may be performed at any visit, if indicated).**

They will take some fluids from your vagina using a swab for research purposes only. They will also take some fluids from your cervix using a swab to test for sexually transmitted infections or sexually transmitted diseases (commonly known as STIs or STDs) and other possible problems if they feel it is necessary. **Some of these swabs may be self-collected. If you are uncomfortable collecting the fluid, a study clinician can collect it for you.**

107. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, Requirement for sexual experience among adolescent enrollees has been removed:*

Ask you questions about your vaginal practices, ~~including sexual activity~~

108. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, edits were made remove the definition of the physical exam & to clarify that some procedures do not occur at each visit and that they are for research purposes:*

~~Perform a physical exam; which will include measuring your height, weight, temperature, pulse, blood pressure, and perform other procedures, as needed~~ **at some visits**

Take a sample of your blood **at some visits**

Check the health of the blood, liver and kidneys ~~at your final visit.~~

~~a~~ **A** pelvic examination:

~~The study doctor or nurse will use a speculum for this exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine the vagina and the cervix during the exam.~~ **be performed at some visits:**

They will take some fluids from your vagina using a swab **for research purposes only.**

During ~~thesome~~ pelvic examinations, a vaginal wash will be performed.

109. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, reference to a speculum exam was removed:*

~~a~~ **A** pelvic examination:

~~The study doctor or nurse will use a speculum for this exam. A speculum is a plastic or metal tool used to help open the vagina so that the doctor or nurse can examine the vagina and the cervix during the exam.~~ **be performed at some visits:**

110. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, sentence about dispensing an oral medication to treat STIs/STDs was removed:*

~~If you are found to have an STI, STD or other health issues, you may be asked to use an oral medication rather than a vaginal medication.~~

111. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, clarifies that the exam to check the positioning of the ring only occurs as necessary:*

Have an exam to ensure that the vaginal ring is properly inserted, **if needed**

112. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, text referring to inquiries about sexual*

activity has been moved/adjusted for clarity:

You may be asked to answer questions that may make you uncomfortable, for example, questions about drug use **or sexual activity**.

113. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? Enrollment and Follow-up Procedures, sentence about reimbursement for text messages was removed:*

~~Information will be given to you regarding reimbursement for text messages in a later section.~~

114. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes?, text about possible infection was modified for clarity:*

At any time during the study, the following may need to be collected if you are having symptoms of **infection**, or if clinicians suspect you may have an infection:

115. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? In-depth Interview Subset, subject N was changed:*

About ~~406~~ teenage girls from each site will participate in the in-depth interview portion of this study.

116. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, What procedures will be performed for research purposes? In-depth Interview Subset, text about participants being asked about how the ring affects their interactions with their partner was modified for clarity:*

Additionally you will be asked about how your vaginal ring use was affected by your home setting, relationships with your friends and/or ~~sex partner~~ **boyfriend(s) or girlfriends**, and your experience with sex (if you are currently sexually active), ~~and your sex partner's response to your vaginal ring use.~~

117. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Pregnancy, Requirement for sexual experience among adolescent enrollees has been removed:*

~~You~~ **Even if you are not currently sexually active, you** must agree to use an effective method of birth control (e.g. birth control pills, hormonal-based methods, intrauterine device (IUD), the patch) but you cannot use a vaginal ring for birth control.

118. *Appendix IV: SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED CONSENT FORM, Risks of Study Drugs, has been updated to reflect the new Investigator's Brochure:*

- Vaginal bleeding **at irregular intervals, particularly between your expected menstrual periods**
- ~~Genital area and/or vaginal itching and/or discomfort~~
- ~~Urinary infection~~
- ~~Vaginal or genital area infection (including vaginal fungal infection)~~
- Vaginal or genital discharge
- ~~Erythema (redness of skin)~~
- **Yeast infection**

- **Urinary tract infection**

119. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Other Possible Risks, Requirement for sexual experience among adolescent enrollees has been removed:*

You may become embarrassed and/or worried when discussing sexual activities **if you are currently sexually active**, ways to protect against HIV and other infections passed through sex, and your test results.

It is also possible for you and/or your partner to feel the vaginal ring during sexual activity-, **if you are currently sexually active**.

120. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, Other Possible Risks, grammatical and other edits made for clarity and comprehensiveness:*

Finding out your HIV status could also cause problems between you and your partner **or your family**.

If you are chosen for the in-depth interview subset, study staff **will** talk with you about how and when you used the study products, **and** they will audio record the discussion using a digital audio recorder.

121. *Appendix III: SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, ASSENT FOR STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION, participant & parent/guardian initialing section has been modified in an effort to align more closely with the standard MTN STORAGE AND FUTURE TESTING OF SPECIMENS and RELATED HEALTH INFORMATION language, also for clarity, to reduce confusion & minor grammar edit was made:*

There might be a small amount of urine, blood, vaginal and cervical fluids 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 leftover urine, blood, vaginal and cervical fluids, and related health information for ~~testing use~~ in future studies. If you agree, your samples **and related health data** will be stored safely and securely. Only approved researchers will have access to the samples. Some employees of the facilities will need to have access to your samples to store them and keep track of where they are, but these people will not have information that directly identifies you. There is no time limit on how long your samples will be stored. **The specific type of testing planned for these specimens is not yet known, however samples may be used by the MTN Laboratory Center to complete additional quality assurance and control testing, ensuring that the tests perform correctly and supply accurate data.** Any future studies testing, ~~beyond the quality assurance and control testing, that may be done~~ will also have to be approved by an Ethics Committee/ Institutional Review Board. **No genetic testing (limited or genome-wide) is planned.** You can still enroll in this study if you decide not to have urine, blood, vaginal and cervical fluids stored for future studies. You can withdraw your assent for the storage and future testing of specimens at any time by providing your request in writing to the person in charge of this study, and the leftover samples will be destroyed. **However, researchers will not be able to destroy samples or information from research that is already underway.**

122. *Appendix IV, SAMPLE INFORMED CONSENT FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE), SAMPLE INFORMED CONSENT, New Information, text about new data being shared with the participant has been removed:*

Researchers working on this study will provide you with ~~any data or~~ new information about HIV

prevention that becomes available, regardless of the product, if it is found to be effective in **adolescent females**.

123. *Appendix IV SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION FORM (SCREENING, ENROLLMENT, and LONG-TERM STORAGE) SAMPLE INFORMED ASSENT & PARENT/GUARDIAN PERMISSION, WHY YOU MAY STOP TAKING THE STUDY DRUG EARLY OR BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT, edit has been made for clarification regarding a final visit if subject chooses to discontinue participating in study:*

In the event that you are removed from or choose to leave this study, you will be asked to return your vaginal ring **and to come back for one final clinic visit**.

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