Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and enrolling participants in MTN-013/IPM 026.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

Approximately 48 women will be recruited across three US sites. The study-wide accrual period is 6 months. Each site-specific accrual period may vary as this period is considered to begin on the first day of participant enrollment at each site. Site staff should make every effort to complete accrual at a rate of about 2-3 participants per month per site. If actual site performance in meeting accrual targets is below the minimum target, the protocol team may determine if the recruitment slots may be made available to another site during the accrual period.

For each site, accrual will begin after all applicable approvals are obtained and a *Site-Specific Study Activation Notice* is issued by the MTN CORE (FHI360).

Once accrual is initiated at each site, study staff will report the following information to the MTN Core (FHI360) on a weekly basis throughout the accrual period:

- Number of participants screened *(participants who sign the IC for screening and per definition in Section 4.2.1 of this manual)*
- Number of participants enrolled *(participants who have been assigned a randomization envelope and randomized to study product)*
- Reasons for screen failures/discontinuation *(participants who sign the IC for screening but have not been enrolled)*
- Number of participants who have completed follow up

Based on this information, the MTN CORE (FHI360) will distribute a consolidated site accrual report to the Protocol Team. In addition, the SDMC will provide the Protocol Team with online access to a report on site accrual information based on data received and entered into the study database.

Site staff are responsible for establishing a study specific participant accrual plan in the form of a SOP on Participant Accrual and updating the SOP and recruitment efforts undertaken if needed to meet site-specific accrual goals. The accrual SOP minimally should contain the following elements:

- Site-specific accrual targets
- Methods for tracking actual accrual versus accrual targets
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Screening and Enrollment

Screening and enrollment procedures are described in detail in Sections 7.1 and 7.2 of the protocol and visit checklists contained in Section 7 of this manual. Informed consent procedures are described in Section 5 and instructions for performing clinical and laboratory screening procedures are included in Sections 10 and 12, respectively. Key screening and enrollment topics are described in Sections 4.2.1-4.2.7 below.

4.2.1 Definition of Screening

The term 'screening' refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-013/IPM 026. It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. The screening and enrollment procedures are described in protocol Sections 7.1 and 7.2. Appendices 4-1 and 4-2 provide further information on the timing of assessment for each eligibility criterion. Sites will be provided with an Eligibility Checklist document (in Word format). This checklist will be utilized to document participant eligibility for study participation. The Eligibility Checklists (Appendices 4-1 and 4-2) will be available on the MTN-013/IPM 026 webpage under the Study Implementation section.

Each study site must establish an SOP that describes how study staff will fulfill this responsibility. This SOP for Participant Eligibility should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment
  - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact mtn013mgmt@mtnstopshiv.org for guidance on subsequent action to be taken.

Note: Women who fail their first screening attempt for any reason may be rescreened a maximum of one time. For example, if all screening and enrollment procedures are not completed with the 45-day screening period, the participant may be re-screened once. If the participant fails to enroll during the re-screening attempt, she cannot be re-screened again and cannot be enrolled in the study.

4.2.2 Definition of Enrollment

Participants will be considered 'enrolled' when they have been assigned a MTN-013/IPM 026 Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 4.2.7.

Note: All Enrollment Visit procedures must be conducted on the same day with the exception of obtaining the enrollment informed consent, which may be obtained at a prior date. If the enrollment informed consent is obtained on a prior date, sites need to pay close attention to the screening to enrollment window and ensure the enrollment process takes place within 45 days of participant signing the informed consent.

4.2.3 Screening and Enrollment Timeframe

Screening may occur anytime and in multiple visits, if necessary, after the informed consent for screening is signed. Written informed consent for screening will be obtained before any screening procedures are initiated. For participants who do not meet the eligibility criteria, screening will be discontinued once ineligibility is determined. Final eligibility determination and Enrollment (Day 0), however, must occur no more than 45 days following provision of informed consent for screening.

Figure 4-1 presents an example of a calendar view of a potential participant who signs or marks her screening informed consent form on 08 August 2011 and indicates that she could be enrolled on any day up to and including 22 September 2011.

Figure 4-1
Example Screening and Enrollment Calendar

August 2011

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
7	8 Screening Date	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

September 2011

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22 Last Day to Enroll	23	24
25	26	27	28	29	30	

To help ensure that the 45-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening visit checklist (as shown in Section 7 of this manual). The SDMC will also provide sites with an Excel Tool (as part of the Visit Calendar Tool) that can be used to determine the last possible day for enrollment for each participant

If all screening and enrollment procedures are not completed up to 45 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the screening informed consent process. The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time the participant provides written informed consent for screening). Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case.

4.2.4 Screening and Enrollment Log

The DAIDS policy on *Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on a Screening and/or Enrollment Log. Screening and Enrollment logs may be maintained separately or combined into one log but must be maintained manually in hard copy to ensure changes and/or updates are completed in real time. Copies of the Screening and Enrollment Log may be maintained electronically.

Figure 4-2 presents a sample screening and enrollment log (combined) suitable for use in MTN-013/IPM 026.

Figure 4-2
MTN-013/IPM 026 Screening and Enrollment Log

No.	Screening Attempt	Screening Date(s)	Participant ID (PTID)	Enrollment date (NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/Discontinuation (or NA if enrolled)	Staff Initials and Date

4.2.5 Assignment of Participant ID Numbers

The MTN SDMC (SCHARP) will provide each study site with a list of Participant ID numbers for use in MTN-013/IPM 026 (PTID-Name Linkage Log). As shown in Figure 4-3, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site.

Further information regarding the structure of PTIDs for MTN-013/IPM 026 can be found in Section 13 of this manual. PTIDs will be assigned to all potential participants who provide written informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes.

Site staff are responsible for establishing a SOP and staff responsibilities for the proper storage, handling, and maintenance of the PTID list such that participant confidentiality maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-3
Sample Site-Specific PTID-Name Linkage Log for MTN-013/IPM 026

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-000010-Z			

4.2.6 HIV Testing

HIV infection status at screening and enrollment will be assessed using an FDA-Approved Enzyme Immunoassay (EIA), as illustrated in Appendix II of the protocol. Guidelines for performing HIV tests during screening and enrollment are provided in Section 12 of this manual.

4.2.7 Syphilis Testing

Syphilis testing will be performed using an FDA approved rapid plasma reagin (RPR) screening test followed by a confirmatory test. All positive RPR results must have a titer obtained and reported. RPR tests may be performed on either serum or plasma. All testing and QC procedures must be performed and documented in accordance with study site SOPs. For reactive RPR tests observed during screening, a confirmatory test result must be received. If a confirmation test is positive, then the participant will not be eligible for enrollment. Appropriate clinical management should include repeat RPR tests at quarterly intervals following syphilis diagnosis to confirm treatment effectiveness. Please consult the MTN NL with any questions related to Syphilis testing to confirm treatment effectiveness and/or interpretation of unusual test results. Questions related to result interpretation in relation to eligibility and enrollment in the study should be directed to the MTN-013/IPM 026 Protocol Safety Physicians (mtn013safetymd@mtnstopshiv.org).

4.2.8 Random Assignment

Each participant will be randomly assigned to one of four vaginal ring product groups.

After the participant's eligibility is confirmed, the participant may be enrolled (randomized) by assigning her a MTN-013/IPM 026 Randomization Envelope. The study is double-blinded, meaning clinic staff, pharmacy staff and study participants do not know which specific vaginal ring product the participant has been assigned.

The SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-013/IPM 026 Randomization Envelope (Appendix 4-3)
- MTN-013/IPM 026 Randomization Envelope Tracking Record (Appendix 4-4)
- MTN-013/IPM 026 Prescription (Appendix 4-5)
- MTN-013/IPM 026 Vaginal Ring Request Slip (see SSP Section 6, Appendix 6-1)

MTN-013/IPM 026 Randomization Envelopes will be shipped from the SDMC to each study clinic. They will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Envelopes must be assigned in sequential order and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with a security tape to ensure envelopes are not tampered with or opened prior to assignment to a participant.

Envelope assignment to eligible participants will be documented on the MTN-013/IPM 026 Randomization Envelope Tracking Record (Section Appendix 4-4). The act of assigning a MTN-013/IPM 026 Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once the Randomization Envelope is assigned, the participant is considered 'enrolled' in the study

4.2.7.1 Prescription Overview

Each Randomization Envelope will contain a prescription. Prescriptions will be produced as two-part no carbon required (NCR) forms pre-printed with the site (CRS) name, DAIDS site ID number, site (CRS) location, randomization envelope number, post-product tear test strip/cervical tissue PK collection (Day 31, 35, or 42) PK/PD sampling assignment. All prescriptions will have the assignment "MTN-013/IPM 026 Vaginal Ring", as all participants will receive a vaginal ring, and the Randomization Envelope Number will indicate to the pharmacy which ring should be dispensed to the participant.

4.2.7.2 Participant-Specific Procedures

For each participant, random assignment will take place after the participant has been confirmed as eligible and has completed the following procedures at the Enrollment Visit:

- CASI Baseline Questionnaire
- Blood collection for plasma archive

The in-clinic randomization procedures are listed below.

In Clinic:

C1. Obtain the next sequential MTN-013/IPM 026 Randomization Envelope and inspect to verify the correct envelope has been obtained and there is no evidence that the envelope has previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the MTN-013/IPM 026 Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and authorized clinic staff initials in the row corresponding to the assigned envelope number.

C2. Open the assigned Randomization Envelope or allow the participant to open it herself. Remove the prescription and confirm the information pre-printed at the top of the form. In particular, confirm that the envelope number printed on the prescription corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, immediately contact the MTN-013/IPM 026 Management Team (mtn013mgmt@mtnstopshiv.org). Do not proceed with randomization of this or any other participant until instructed to do so by the SDMC.

C3. Inform the participant of her post-product tear test strip/cervical tissue PK sampling assignment (i.e. Day 31, 35, or 42).

C4. Complete the prescription as follows:

In the top section of the prescription, record the PTID and mark whether the participant provided informed consent to take part into the study. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572.

The bottom section of the prescription indicates date the randomization envelope was opened and may be completed by any clinic staff member.

C5. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook. Also retain the MTN-013/IPM 026 Randomization Envelope in the participant study notebook.

C6. Deliver the white (pharmacy) original prescription to the study pharmacy. This may be done by the participant or by a study staff member.

In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions, and fully documented in the participant's chart notes.

4.2.9 Product Use Instructions, First Product Use and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions regarding vaginal ring insertion, followed by adherence counseling. Participants also will insert the VR at the clinic during their enrollment visit. Following insertion of the VR, the study clinician should check placement of the VR, regardless of who inserted it, to confirm correct placement. Further guidance related to product use instructions, first product use, and adherence counseling is provided in Section 17 of this manual.

Section Appendix 4-1
Eligibility Checklist for MTN-013/IPM 026 Inclusion Criteria

PTID: _____

Inclusion Criteria	Screening Visit Staff Int./Date	Enrollment Visit Staff Int./Date
Age 18 through 40 years (inclusive) at screening, verified per site SOPs		
Able and willing to provide written informed consent to be screened for and take part in the study		
Able and willing to provide adequate locator information, as defined by the site SOPs		
HIV-uninfected, based on testing performed by study staff at Screening and Enrollment (per applicable algorithm in Appendix II)		
In general good health at Screening and Enrollment, as determined by the site IoR or designee		
At Screening, participant states willingness to abstain from receptive sexual activity (including oral, vaginal and anal intercourse) for the 14 days prior to enrollment and for the duration of study participation		
Per participant report, using an effective method of contraception at Enrollment, and intending to continue use of an effective method for the duration of study participation. Effective methods include hormonal methods (except contraceptive vaginal rings), intrauterine device (IUD) inserted at least 28 days prior to enrollment, being a woman who identifies as a woman who has sex with women exclusively, sterilization, and/or sexually abstinent for the past 90 days		
Satisfactory Pap result in the 12 calendar months prior to Enrollment consistent with Grade 0 according to the Female Genital Grading Table for Use in Microbicide Studies Addendum 1 to the DAIDS Table for Grading Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), or satisfactory evaluation with no treatment required of Grade 1 or higher Pap result per American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines in the 12 calendar months prior to Enrollment.		
Per participant report at Screening and Enrollment, agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the duration of study participation		
Per participant report at Screening, regular menstrual cycles with at least 21 days between menses (does not apply to participants who report using a progestin-only method of contraception at screening, e.g., Depo-Provera or levonorgestrel-releasing IUD) *Note: This criterion is not applicable to participants using continuous combination oral contraceptive pills, as the absence of regular menstrual cycles is an expected, normal consequence in this context*		
At Screening and Enrollment, participant states a willingness to refrain from inserting any non-study vaginal products or objects into the vagina, including but not limited to, spermicides, female condoms, diaphragms, contraceptive vaginal rings, vaginal medications, menstrual cups, cervical caps (or any other vaginal barrier method), douches, lubricants, sex toys (vibrators, dildos, etc.), and tampons for the 5 days prior to enrollment throughout the duration of study participation. *Note: At the Screening visit participant also agrees to refrain from the practices listed above for at least 5 days prior to enrollment.*		

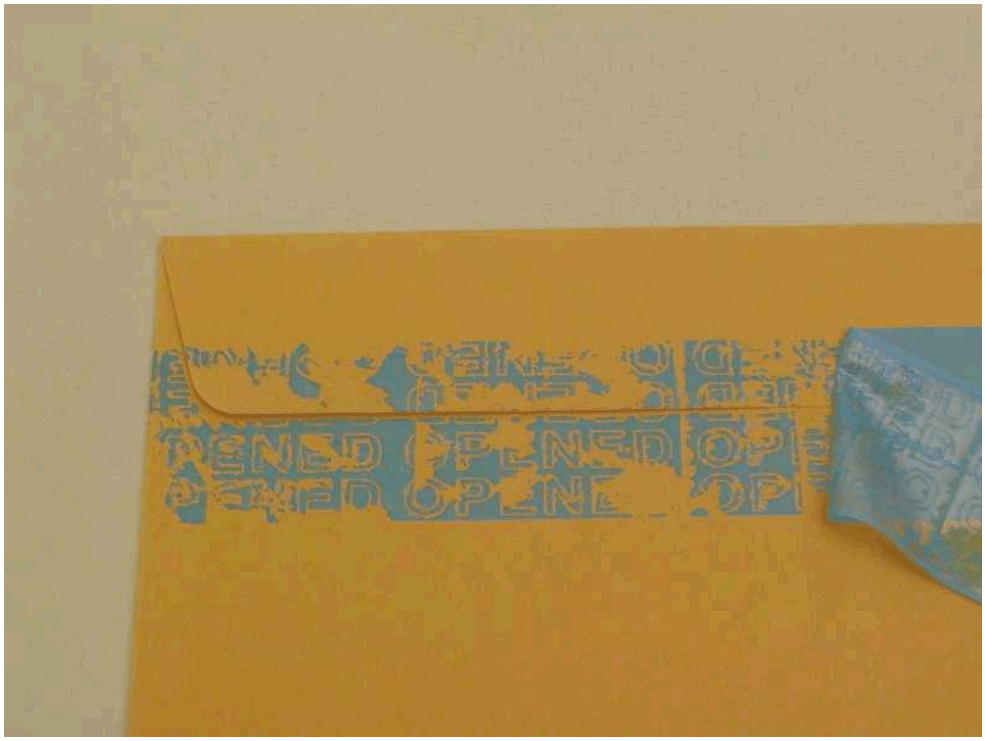
Section Appendix 4-2
Eligibility Checklist for MTN-013/IPM 026 Exclusion Criteria

PTID: _____

Exclusion Criteria	Screening Visit Staff Int./Date	Enrollment Visit Staff Int./Date
Participant report of any of the following at Screening: a. Known adverse reaction to silicone, titanium dioxide, or to any of the components of the study products b. Use and/or anticipated use during the period of study participation of CYP3A inducer(s) and/or inhibitor(s) c. Chronic and/or recurrent candidiasis d. Non-therapeutic injection drug use in the 12 months prior to screening e. Post-exposure prophylaxis for HIV exposure within 6 months prior to screening f. Last pregnancy outcome 90 days or less prior to screening g. Currently breastfeeding h. Hysterectomy i. Intends to become pregnant within the next 4 months j. Has plans to relocate away from the study site area in the next 4 months		[redacted]
Reports participating in any other research study involving drugs, medical devices, or vaginal products 60 days or less prior to enrollment		
At Screening or Enrollment, as determined by the IoR/designee, any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, or at increased risk of cardiovascular events		
Has any of the following laboratory abnormalities at Screening: a. Aspartate aminotransferase (AST) or alanine transaminase (ALT) Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009) b. Calculated creatinine clearance less than 60 mL/min by the Cockcroft-Gault formula, where creatinine clearance (female) in mL/min = (140 – age in years) x (weight in kg) x (0.85)/72 x (creatinine in mg/dL) c. Hemoglobin Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009) d. Platelet count Grade 1 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009) e. White blood cell count Grade 2 or higher as per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events Version 1.0, December, 2004 (Clarification dated August 2009) f. Positive HBsAg test result g. Positive Anti-HCV test result		[redacted]

Note: Otherwise eligible participants with an exclusionary test result may be re-tested during the screening process. If a participant is re-tested and a non-exclusionary result is documented within 45 days of providing informed consent for screening, the participant may be enrolled.		
At Screening or Enrollment, is pregnant		
Diagnosed with urinary tract infection (UTI) at Screening or Enrollment[3] *Note: Otherwise eligible participants diagnosed with UTI during screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.*		
Diagnosed with pelvic inflammatory disease, a sexually transmitted infection (STI) or reproductive tract infection (RTI) requiring treatment per current Centers for Disease Control and Prevention (CDC) guidelines (http://www.cdc.gov/std/treatment/) at Screening or Enrollment *Note: Otherwise eligible participants diagnosed with STI or RTI during screening will be offered treatment and may be enrolled after completing treatment and all symptoms have resolved. If treatment is completed and symptoms have resolved within 45 days of obtaining informed consent for screening, the participant may be enrolled.*		
At Screening or Enrollment, has a clinically apparent Grade 1 or higher pelvic exam finding (observed by study clinician or designee) per the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, December 2004 (Clarification dated August 2009), Addendum 1, Female Genital Grading Table for Use in Microbicide Studies *Note: Cervical friability bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding and is not exclusionary.*		
At Screening, severe pelvic relaxation such that either the vaginal walls or the uterine cervix descend beyond the vaginal introitus with valsalva maneuver		
Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving study objectives		

Section Appendix 4-3
MTN-013/IPM 026 Randomization Envelopes



Section Appendix 4-4
MTN-013/IPM 026 Randomization Envelope Tracking Record

CRS Name:	**Pre-printed**	DAIDS Site ID:	**Pre-printed**
CRS Location:	**Pre-printed**		

Instructions: Complete one row each time a MTN-013/IPM026 randomization envelope is assigned to a study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

MTN013/IPM026 Randomization Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (hh:mm) (24-hour clock)	Clinic Staff Initials
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				
Pre-printed				

Section Appendix 4-5
MTN-013/IPM 026 Prescription

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-printed**	**DAIDS Site ID:**	**Pre-printed**
CRS Location:	**Pre-printed**	**Randomization Envelope #:**	**Pre-printed**

Post-product tear test strip/cervical tissue PK collection assignment:	**Pre-printed**

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did the participant provide written informed consent for enrollment into MTN-013/IPM 026?..... Yes ☐ No ☐ Clinic Staff Initials _____

MTN-013/IPM 026 Vaginal Ring

SIG: Insert one study ring into the vagina at the Enrollment Visit. Leave the ring in place for 28 consecutive days. Refill only one additional vaginal ring if needed.

Quantity: One vaginal ring. Refill only one additional vaginal ring if needed.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd MMM yy

Clinic Staff Instructions: Complete all items on this prescription. After initialing and dating below, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ Date: ☐☐–☐☐☐–☐☐
dd MMM yy