Section 6. Participant Follow-up

This section provides information on requirements and study visit procedures for participant in follow-up.

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through 7 ½ weeks after the date of enrollment. The target accrual is expected to be completed within six months of site activation. The protocol team will actively monitor study accrual to ensure enrollment occurs within the specified timeframe. Each enrolled participant will be followed through to the scheduled Day 52 Final Clinic/Termination Visit, which will occur on Day 52.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants. Further information on MTN-013/IPM 026 retention definitions and procedures is provided in Section 8.

6.2 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted:

- **Scheduled visits** are those study visits required per protocol. The protocol specifies that, after Screening and Enrollment, follow-up visits are targeted to occur on visit days 1, 2, 3, 5, 7, 14, 21, 28, 29, 30, 31, 35, 42 and 52. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13.

- **Interim visits** are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place. Interim visits may be performed at any time during the study, for the following or other reasons:
    - For product-related reasons, e.g., a participant may need a replacement vaginal ring or want to discuss problems with adherence to product use.
    - In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant to appropriate medical care (see also Section 9).
    - For interim STI counseling and testing in response to STI symptoms or interim HIV counseling and testing in response to presumed exposure to HIV or to provide participants with the results of confirmatory HIV test results.

All interim contacts and visits will be documented in participants' study records and on applicable CRFs. Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13.

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Follow-up visits are targeted to occur as outlined in Figure 6-1 and are based on the participant's study enrollment date, which is the date the participant is assigned an MTN-013/IPM 026 Randomization Envelope. The MTN Statistical and Data Management Center (SDMC) will provide each site with a visit scheduling tool that can be used to generate follow-up visit schedules for enrolled participants. This tool will be available on the available on the MTN-013/IPM 026 webpage under the Study Implementation section.

6.3.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-013/IPM 026 protocol allows for certain visits to be completed within a visit window. Figure 6-1 illustrates the visit windows established for this study. Figures 6-2 and 6-3 illustrate the target visit dates (calendar view) for a sample study participant.

Sites are encouraged to complete required study visits on the target day if at all possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals, and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine retention reports for purposes of monitoring adherence to the weekly visit schedule (see Section 15).

Figure 6-1
Follow-up Visit Target Dates and Visit Windows

Visit Day	Follow-up Visit	Target Study Day	Visit Window (Day Open/Day Close)	
			Window Opens	Window Closes
Day 1	3.0	1	No visit window	
Day 2	4.0	2	No visit window	
Day 3	5.0	3	No visit window	
Day 5	6.0	5	5	6
Day 7	7.0	7	7	8
Day 14	8.0	14	13	15
Day 21	9.0	21	20	22
Day 28	10.0	28	No visit window	
Day 29	11.0	29	No visit window	
Day 30	12.0	30	No visit window	
Day 31	13.0	31	31	32
Day 35	14.0	35	34	36
Day 42	15.0	42	41	43
Day 52/Final Clinic/Termination	16.0	52	51	53

Figure 6-2
Follow-up Visit Target Dates and Visit Windows for a Sample Participant

August 2011						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	2	3	4	5	6
7	8	9 Enrollment Date	10 Day 1	11 Day 2	12 Day 3	13
14 Day 5	15 Day 5 Window Closes	16 Day 7	17 Day 7 Window Closes	18	19	20
21	22 Day 14 Window Opens	23 Day 14	24 Day 14 Window Closes	25	26	27
28	29 Day 21 Window Opens	30 Day 21	31 Day 21 Window Closes			
September 2011						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6 Day 28	7 Day 29	8 Day 30	9 Day 31	10 Day 31 Window Closes
11	12 Day 35 Window Opens	13 Day 35	14 Day 35 Window Closes			17
18	19 Day 42 Window Opens	20 Day 42	21 Day 42 Window Closes			24
25	26	27	28	29 Day 52 Window Opens	30 Day 52	1 Day 52 Window Closes

Figure 6-3
Follow-up Visit Target Dates and Visit Windows for a Sample Participant

Visit Day	Follow-up Visit	Target Study Day	Target Visit Date	Visit Window	
				Window Opens	Window Closes
Day 1	3.0	1	10 August	No visit window	
Day 2	4.0	2	11 August	No visit window	
Day 3	5.0	3	12 August	No visit window	
Day 5	6.0	5	14 August	Same Day	15 August
Day 7	7.0	7	16 August	Same Day	17 August
Day 14	8.0	14	23 August	22 August	24 August
Day 21	9.0	21	30 August	29 August	31 August
Day 28	10.0	28	06 September	No visit window	
Day 29	11.0	29	07 September	No visit window	
Day 30	12.0	30	08 September	No visit window	
Day 31	13.0	31	09 September	Same Day	10 September
Day 35	14.0	35	13 September	12 September	14 September
Day 42	15.0	42	20 September	19 September	21 September
Day 52/Final Clinic/Termination	16.0	52	30 September	29 September	01 October

6.3.3 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed on a single day. In the event that all required procedures cannot be completed on a single day (e.g. a participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the visit window (for visits with a window). When this happens, it is referred to as "split visit" (required visit procedures are split across more than one day within the visit window). PK specimens (blood, tear test strip, and cervical tissue) and applicable CASI questionnaires should always be collected on the same day to avoid complicating interpretability. If it is not possible to do so, the site should reschedule the participant to come back within the visit window to complete these PK specimen collection and CASI behavioral procedures. If sites have any questions about PK specimen collection timing in cases where a visit has to be rescheduled, they should consult the PSRT via a PSRT Query Form (located in Section Appendix 11-2 of this manual as well as on the MTN-013/IPM 026 webpage under Study Implementation Materials).

6.3.4 Missed Visits

When a participant does not complete any part of a scheduled visit within the visit window, the visit is considered "missed" and a Missed Visit form is completed. Section 13 gives detailed information regarding the completion of the Missed Visit form. If no part of the visit is completed within the window, the visit is considered "missed" and must be documented using a Missed Visit DataFax CRF. If the visit does not have a window, for example, the Day 1 Visit only the target visit is considered "missed" if no part of the visit is completed on the target day.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.3, 7.4 and 7.5. Several additional clarifications of the procedural specifications in protocol Section 7.5 are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures at follow-up visits is incorporated into the visit checklists which is included in Section 7 of this manual.

6.5 Follow-up Visit Locations

Because of the nature of study procedures required to be performed at MTN-013/IPM 026 follow-up visits, all visits are to be completed at the study clinic.

6.6 Participant Transfers

The transfer of participants is not expected to occur, but the following instructions are provided should the rare participant transfer occur.

During the course of the study, participants may leave the area in which they enrolled in the study and re-locate to another area where the study is taking place. To maximize participant retention, participants who re-locate from one study location to another should be encouraged to continue their study participation at their new location. To accomplish this, study staff at both the original site (called the "transferring" site) and the new site (called the "receiving" site) will complete the process of a participant transfer.

Upon identifying a need for a participant transfer, the transferring site will notify the receiving site as well as the MTN-013 Management Team for further instructions.

6.7 Product Re-Supply during Follow-up

Each participant will receive a vaginal containing 25 mg dapivirine, or 100 mg maraviroc, or 25 mg dapivirine + 100 mg maraviroc or placebo at their Enrollment Visit. Participants should be instructed to wear the ring for 28 consecutive days. At the Day 28 visit, the ring will be removed by the study clinician.

Note: In the event the ring is removed by the participant or the ring comes out involuntarily (expelled) prior to the Day 28 visit, the participant should be instructed to rinse the ring with clean warm water and re-insert immediately. If the participant is unable and/or unwilling to re-insert the ring, she should be instructed to notify site staff immediately. The participant should be instructed to rinse the ring with clean warm water, pat dry with a paper towel, and place in the study-provided re-sealable plastic bag or suitable substitute, until the participant is able to return to the study clinic. When the ring is returned, the site clinician will determine if the used ring will be re-inserted. The ring should be rinsed with clean warm water prior to reinsertion by either the participant or the site clinician.

At each follow-up visit, during the vaginal ring use period, study staff will determine whether a participant remains eligible for continued study product use per specifications listed in section 9 of the protocol. These sections list conditions under which ring use should be held, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

6.7.1 Temporary Hold

If a temporary hold of the vaginal ring is deemed clinically necessary, as determined by the site clinician, the vaginal ring should be rinsed with clean warm water, pat dry with a paper towel, and placed in the study-provided re-sealable plastic bag and returned to the study participant. A MTN-013/IPM 026 Vaginal Ring Request Slip should be completed and delivered to the pharmacy to inform the site pharmacist. Site staff should mark 'HOLD' and include the reason for the hold (i.e. in response to an AE). A Product Hold/Discontinuation Log case report form should also be completed to document the hold of ring use and faxed to SCHARP.

If vaginal ring use is resumed, the participant should be instructed to re-insert the vaginal ring. If re-instatement occurs during a scheduled study visit, the clinician should check the vaginal ring prior to the participant re-inserting. If re-instatement occurs outside of a scheduled study visit, participant should check the vaginal ring prior to re-inserting. The Vaginal Ring Request Slip should be updated and marked 'RESUME' and delivered to the pharmacy to inform the site pharmacist. The Product Hold/Discontinuation Log case report form should be updated accordingly and re-faxed to SCHARP.

6.7.2 Permanent Discontinuation

Vaginal ring use must be permanently discontinued if the ring has been out longer than three (3) days. Ring use must also be permanently discontinued in response to certain AEs (see sections 9.3-9.7). If it is determined by the site clinician that study product use will be permanently discontinued, site staff should complete a MTN-013/IPM 026 Vaginal Ring Request Slip. Site staff should mark 'Permanent Discontinuation' and include the reason for discontinuation (i.e. due to a clinical reason or because the ring has been out for longer than 3 days). A Product Hold/Discontinuation Log case report form should also be completed to document the permanent discontinuation and faxed to SCHARP. Participants who are permanently discontinued from ring use will be offered the option to continue in follow-up per their original study schedule. If the participant opts to remain in follow-up, all the protocol specified study procedures will continue with the exception of the following:

- Provision of study product
- Pelvic exams*
- PK specimen collection (blood and pelvic samples)
- Provision of adherence counseling
- Acceptability, Protocol Adherence, and Product Use Adherence assessments

*Unless required for AE follow-up

6.7.3 Product Handling

Used rings should never be returned to the pharmacy. Site staff will document collection of the used (original and /or replacement) ring on the Follow up Visit or Interim Visit case report form, as applicable (item 4). Site specific product handling guidelines are outlined below.

Alabama and Fenway Only (Residual Drug Analysis): Vaginal rings collected from the participant should be prepared for the appropriate laboratory testing per Section 12 of this manual. These include the original and/or any replacement ring provided to the study participant.

- All (original and replacement) rings removed by the study clinician from the participant at their scheduled Day 28 visit.
- All (original and replacement) rings removed by the study clinician as a result of permanent discontinuation of ring use at any scheduled or interim visit (i.e. AE or out longer than 3 days).
- All (original and replacement) rings which are removed and returned by the participant prior to the Day 28 visit and will not be re-inserted.
- All (original and replacement) rings which are involuntarily expelled prior to the Day 28 visit and will not be reinserted.

Pittsburgh (Biofilm Assessment and Residual Drug Analysis): Vaginal rings removed by the study clinician from the participant should be prepared for the appropriate laboratory testing (biofilm assessment or residual drug analysis) per Section 12 of this manual. These include the original and/or any replacement ring provided to the study participant. Note: Given targeted enrollment for the Pittsburgh site will increase to 24 participants (the original 16 plus an additional 8 participants). Vaginal rings supplied to the additional 8 participants should be prepared for residual drug analysis.

- All (original and replacement) rings removed by the study clinician from the participant at their scheduled Day 28 visit. The ring should not be rinsed prior to preparing it for biofilm assessment
- All (original and replacement) rings removed by the study clinician as a result of permanent discontinuation of ring use at any scheduled or interim visit (i.e. AE or out longer than 3 days)
- All (original and replacement) rings which are involuntarily expelled or which are removed and returned by the participant (prior to the Day 28 visit) and will not be re-inserted should be prepared for residual laboratory testing per Section 12 of this manual.

6.7.4 Replacement Ring

Replacement rings will be provided at the discretion of the site IoR or designee and determined on a case by case basis. If, at the discretion of the site IoR or designee, a replacement ring will be provided to the participant, site staff should complete the MTN-013/IPM 026 Vaginal Ring Request Slip (unless other hold criteria are met). Site staff should mark 'RESUPPLY' and include the reason for re-supply. The completed Vaginal Ring Request Slip should be delivered to the site Pharmacist to inform him/her that one vaginal ring should be dispensed.

6.7.5 Discoloration of the Vaginal Ring

If at any time during the study, discoloration of the vaginal ring is identified (either by participant-report or clinician assessment during a pelvic exam), site staff should notify the MTN-013/IPM 026 PSRT immediately for guidance on product use and/or clinical management. Site staff should consult the PSRT via a PSRT Query Form (located in Section Appendix 11-2 of this manual as well as on the MTN-013/IPM 026 webpage under Study Implementation Materials). When notifying the PSRT, site staff should include all relevant details including any abnormal conditions or signs/symptoms as well as an interval update on the participants medical/menstrual history, contraceptive method, and use of concomitant medications.

6.8 MTN-013/IPM 026 Vaginal Ring Request Slip

The MTN-013/IPM 026 Vaginal Ring Request Slip (Section Appendix 6-1) is a two-part no carbon required (NCR) document. In the event that a participant requires a replacement ring, the initial prescription indicates one replacement vaginal ring may be dispensed. In order for the participant to receive a replacement ring, the Vaginal Ring Request Slip must be completed by the clinic staff to inform the pharmacy to dispense (re-supply) one vaginal ring. The Vaginal Ring Request Slip will also be used to inform the pharmacy if product needs to be held (permanently or temporarily) or resumed. Section 9 of this manual contains detailed information on clinic staff procedures for the dispensation of study product, as well as the return of used study products.

The Vaginal Ring Request Slip should be completed as follows:

- Record the clinic name.
- Record the PTID assigned to the participant and the Randomization Envelope Number in the boxes provided.
- Mark the box for RESUPPLY, HOLD, RESUME or PERMENANT DISCONTINUATION, to indicate the action to be taken by the study pharmacy.
    - *If RESUME is marked but the original ring will be reinserted, site staff should draw a single line through the note 'Pharmacy: Dispense one vaginal ring' and initial and date.*
- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order product supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Study Product Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.
- Double-check the accuracy of all entries and then separate the two parts of the completed Vaginal Ring Request Slip. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

6.9 HIV Testing during Follow Up

During follow-up, HIV testing will be performed on all participants at the Final Clinic/Termination Visit (Day 52). Testing will also be performed if clinically indicated at the Day 28, 31, 35, and 42 visits. HIV testing will be performed according to the algorithm in protocol Appendix II. Further information on the procedural and documentation requirements of the algorithm is provided in the remainder of this section. Further instructions for performing HIV tests during follow-up are provided in Section 12 of this manual.

All tests must be documented on local laboratory log sheets or other laboratory source documents. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results within the timeframe of the tests and prior to disclosure of results to participants. For positive/reactive results, review, verification, and sign-off must be performed by a nurse, clinician, or physician. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

6.10 Modified Procedures for Participants Who Become Infected with HIV

Refer to protocol sections 7.5.1 9.3 and 9.6.

Participants with a reactive or indeterminate HIV test result should immediately discontinue VR use and be instructed to return the VR within five working days. If product cannot be retrieved within five working days, the PSRT must be informed. Clinic staff should inform pharmacy staff of the product hold in writing, using a Vaginal Ring Request Slip, and should complete and fax a Product Hold/Discontinuation Log form, prior to the participants scheduled study exit, to the MTN SDMC.

- For participants in the VR use period whom HIV infection is confirmed per the algorithm in protocol Appendix II, product use must be permanently discontinued. Clinic staff should inform pharmacy staff of the permanent discontinuation in writing, using the Vaginal Ring Request Slip. Clinic staff should also update the Product Hold/Discontinuation Log form to document the permanent discontinuation and date of permanent discontinuation (i.e., the date site staff informed the participant that her HIV infection was confirmed), then re-fax the form to the MTN SDMC. The PSRT does not need to be notified.
- For participants who are later confirmed HIV-uninfected per the algorithm in protocol Appendix II, product use should continue to be held and the IoR or designee should immediately consult with the PSRT for further guidance. If, in consultation with the PRST, product use is resumed, clinic staff should inform pharmacy staff of the resumption in writing, using a Vaginal Ring Request Slip signed by an authorized prescriber. Clinic staff should also update the Product Hold/Discontinuation Log form to document resumption of product use, and then refax the form to the MTN SDMC.

Participants with confirmed HIV infection will be offered the option to continue follow-up visits per their original study schedule until their originally scheduled study exit date. HIV RNA and drug resistance testing will be performed. All participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons according to the local standard of care. For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to current prevention of mother to child transmission regimens to reduce the probability of HIV transmission to the participant's infant.

HIV infected participants who chose to remain in follow up, all protocol-specified study procedures will continue, with the following exceptions:

- HIV testing
- Provision of study product
- Acceptability, Protocol Adherence, and Product Use Adherence assessments
- Pelvic exams

- PK specimen collection (blood and pelvic samples)
- Provision of counseling (HIV pre/post-test, protocol and product use adherence)
- HIV/STI risk reduction counseling will be modified to address primary and secondary prevention for infected women.

6.11 Modified Procedures for Participants Who Become Pregnant

All study participants are required to be sexually abstinent, including receptive vaginal, oral, and anal sex, during MTN-013/IPM 026. Pregnancy testing will be performed for all participants at Days 14, 28, and Day 52. Testing will also be conducted if indicated at the Day 31, 35, or 42 Visit based on the participant's randomization assignment as well as at all other study visits. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff. The IoR/designee will counsel any participant who becomes pregnant regarding possible risks to the fetus according to site SOPs. The IoR/designee also will refer the participant to all applicable services; however, sites will not be responsible for paying for pregnancy-related care.

Participants who become pregnant during the course of the study will permanently discontinue study VR use but will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to maintain her original follow up schedule and complete all study visits. While in scheduled follow-up, all protocol-specified study procedures including pregnancy testing will continue to be conducted for pregnant participants, with the following exceptions:

- Urine hCG testing
- Provision of study product
- Acceptability, Protocol Adherence, and Product Use Adherence assessments
- Pelvic exams
- PK specimen collection (blood and pelvic specimens)
- Provision of counseling (contraceptive and product adherence)

For participants who become pregnant, a Pregnancy Report form must be completed to report the pregnancy. Participants who are pregnant at the Final Clinic/Termination Visit (Day 52) will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained). A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be ascertained based on participant report. All study sites are strongly encouraged to use a pregnancy management worksheet similar to Section Appendix 6-2 below to ensure proper documentation of the pregnancy and timely discontinuation of VR use.

If the pregnancy occurs during the VR use period, site pharmacy staff must be informed of the product permanent discontinuation in writing using the Vaginal Ring Request Slip. The study VR previously dispensed to pregnant participants must be retrieved as soon as possible after the pregnancy is identified, and a Product Hold/Discontinuation Log form (see Section 13) must be completed and transmitted to the MTN SDMC.

Participants who become pregnant may take part in observational studies, including registries such as HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study (MTN-016) provided the study site is participating in MTN-016.

6.12 Modified Procedures for Participants Who Permanently Discontinue Product Use (IoR Discretion or Participant Volunteer)

Participants who are permanently discontinued from VR use will be instructed to return the study VR. Participants who permanently discontinue product use, either by IoR discretion or voluntarily, during the course of the study will not routinely be withdrawn from the study. Rather, if the participant does not withdraw her consent, every effort will be made to maintain her original follow up schedule and complete all study visits. All protocol-specified study procedures will continue except the following:

- Provision of study product
- Pelvic exams*
- PK specimen collection (blood and pelvic specimens)
- Provision of adherence counseling
- Acceptability, Protocol Adherence, and Product Use Adherence assessments

*Unless required for AE follow-up

6.13 Modified Follow-up Procedures for Participants Who Are Found To Be Infected with Hepatitis B and/or C

Refer to protocol section 9.9. Hepatitis B surface antigen (HBsAg) and Anti-HCV testing is performed for all participants at Screening. For participants who were previously screened and/or enrolled prior to LoA #01, testing must be performed at the participants next scheduled study visit.

Vaginal ring use must be held for participants who develop signs or symptoms of clinical hepatitis during study follow-up. Participants with such signs or symptoms should be tested for hepatitis, including serology for HBsAg and Anti-HCV and any other testing consistent with local standard of care.

Study product use must be permanently discontinued for participants with confirmed Hepatitis B and/or C infection. Participants with confirmed infection will be clinically managed or referred for clinical management according to local standard of care. The IoR or designee may consult with the PSRT on any questions or concerns related to discontinuation of product use or other aspects of clinical management of participants with Hepatitis B or C.

If the infection occurs during the VR use period, site pharmacy staff must be informed of the product permanent discontinuation in writing using the Vaginal Ring Request Slip. Site pharmacy staff should be informed of the product hold in writing, using the Vaginal Ring Request Slip, and a Product Hold/Discontinuation Log form should be completed and faxed to the MTN SDMC.

In the event that a participant is permanently discontinued from study product use, every effort should be made to collect the used VR within five working days. The participant should be asked to report to the study clinic in order for the study clinician to remove the ring.

Every effort will be made to maintain her original follow up schedule and complete all study visits. All protocol-specified study procedures will continue per protocol section 7.5.3. The following procedures will no longer occur:

- Provision of study product and instructions
- Pelvic exams
- PK specimen collection (blood and pelvic specimens)
- Provision of protocol and product use adherence counseling
- Acceptability and Adherence assessments

6.14 Resumption of Study Participation After Voluntary Withdrawal

As stated in protocol section 9.8, regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time. The protocol allows for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned follow-up period, resume study procedures and follow-up at the investigator's discretion.

If such cases arise, study staff are advised to contact the mtn013mgmt@mtnstopshiv.org for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study.

6.15 Study Exit Considerations

Procedural requirements for conducting study exit visits are specified in protocol section 7.4.5; further procedural guidance is incorporated in the Day 52/Final Clinic/Termination Visit checklist in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.15.1 Participant Locator Information

As described in greater detail in Section 8, accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

6.15.2 Counseling and Testing

HIV testing is performed at the Day 52/Final Clinic/Termination. HIV pre- and post-test counseling provided at the study exit visit should emphasize that additional counseling and testing will be provided to the participant after her study exit visit if needed to clarify or confirm her HIV status.

6.15.3 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the Final Clinic/Termination visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to MTN SDMC DataFax.

For any AEs requiring expedited reporting according to (*according to the Manual for Expedited Reporting of Adverse Events to DAIDS, January 2010)* that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow up plan for the AE (see Section 11.1 of this manual for more information on AE reporting and safety monitoring). At a minimum, the AE must be re-assessed by study staff within 30 days after the participant's study exit visit. Additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. It is recommended that AE follow-up plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-3.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30 days after the study end date. The MTN-013/IPM 026 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis.

For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log case report forms based on the re-assessments. All information related to the re-assessment of AEs should be documented in the participant's chart notes, including all efforts to contact the participant.

6.15.4 Final Study Contact

Although the study exit visit is the last scheduled study visit, a final contact is required after the exit visit to provide the participant with her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant at study exit
- Participants with positive or indeterminate HIV Western blot (WB) test results
- Participants with certain types of AEs that are ongoing at study exit

For each participant, a final contact should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. Study staff may complete final contacts at the study site, by telephone, or at community-based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records, but no case report forms are completed for these contacts. It is recommended that final contact plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-3.

6.15.5 Referral to Non-Study Service Providers

After completing their study exit visits and final study contacts, participants will no longer have routine access to services provided through the study, such as reproductive health care and HIV counseling and testing. Participants should be counseled about this —ideally before and during their study exit visits — and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop a sample script which can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their study exit visits (after obtaining IRB/EC approval of the written information). A sample script which may be tailored for use at each site is provided in Section Appendix 6-4.

6.15.6 Early Termination

In the case of early termination, please see section 8.6 of this manual for further instructions on procedures for participants who voluntarily discontinue study participation prior to their scheduled Day 52/Final Clinic Visit.

6.15.7 Post-Study Contact

It is expected that all participants will be re-contacted by study staff approximately three to six months after study completion, when it is expected that study results will be available for dissemination to all participants.

To facilitate post-study contact with participants, locator information should be updated at the study exit visit, and participants should be counseled to contact the study site should their locator information change after study exit. In addition, participant preferences for methods to be used for contacting them when study results are available should be documented in participant study records. It is recommended that participant preferences be recorded on a study exit worksheet similar to the sample provided in Section Appendix 6-3.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-3. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs similar to the examples provided in Section Appendix 6-5.

MTN-013/IPM 026 VAGINAL RING REQUEST SLIP

Clinic Name: _____

Participant ID: ☐☐☐–☐☐☐☐☐–☐ **Randomization Envelope Number:** ☐☐☐

Clinic Staff Instructions: Mark whether this is a study vaginal ring re-supply, hold, resume, or permanent discontinuation request. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook

☐ **RE-SUPPLY** → **Reason:** _____

Pharmacy: Dispense one vaginal ring.

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense further vaginal rings to the participant until another MTN-013/IPM 026 Vaginal Ring Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy:** Dispense one vaginal ring.

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____

Pharmacy: Do not dispense any further vaginal rings to the participant.

Clinic Staff Name (please print): _____

Clinic Staff Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Section Appendix 6-2
Sample Pregnancy Management Worksheet

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated week 16 and full term pregnancy dates		**Week16:**	**Full Term:**
PREGNANCY MANAGEMENT INFORMATION		**Mark ✓ When Done**	**Initials/Date/Comments**
1	**Follow Up or Interim form completed and faxed to SCHARP**		
2	**Participant instructed to HOLD product use and return vaginal ring to clinic (N/A if no vaginal ring to retrieve)**		
3	**Pregnancy Report form completed and faxed to SCHARP**		
4	**Pharmacy informed of permanent discontinuation of product use via Vaginal Ring Request Slip (if prior to Day 28 Visit)**		
5	**Product supplies retrieved from participant and prepared for Network Lab analyses**		
6	**Product Hold/Discontinuation form completed and faxed to MTN SDMC (if prior to Day 28)**		
7	**Participant referred for antenatal care (or MTN-016 if applicable)**		
8	**Pregnancy outcome and outcome date ascertained, based on:** **❒ medical records or other written documentation from a licensed non-study health care practitioner** **❒ participant self-report** **❒ negative pregnancy test performed by study staff** **❒ other (specify in comments)** ***(medical records should be obtained whenever possible)***		
9	**Pregnancy Outcome form completed and faxed to MTN SDMC**		
10	**If applicable, AE Log form completed and faxed to MTN SDMC**		
11	**If applicable, EAE Report completed via DAERS**		

Section Appendix 6-3
Study Exit Worksheet

PTID:	**Exit Visit Date:**
Plan for providing participant with final study test results	
Method by which participant wishes to be contacted when study results are available	
Does participant have study product remaining in her possession? ❒ No, per participant report, all product supplies have been used/collected/returned ❒ Yes ⇒ describe plan for product collection (continue on back if needed) ❒ Completed _____	
Is participant currently pregnant? ❒ No ❒ Yes ⇒ describe plan for ascertaining pregnancy outcome (continue on back if needed) IoR approval: _____ ❒ Completed: _____	
Does participant have any ongoing SAEs/EAEs or any AEs at this visit? ❒ No ❒ Yes ⇒ describe plan for AE follow-up (continue on back if needed) IoR approval: _____ ❒ Completed: _____	
Is participant willing to be contacted about future studies for which she may be eligible? ❒ No ❒ Yes	
Staff Signature and Date:	

Section Appendix 6-4
Sample Script for Study Exit Visits

Before we finish your visit today, I would like to take some time to sincerely thank you for taking part in this study. By taking part, you have made an important contribution to the fight against HIV/AIDS.

I also would like to review a few more details with you:

- *If applicable, reinforce plans to collect remaining product supplies.*

Your appointment to receive your final exam and test results is scheduled for [insert date]. This appointment will take place here at the clinic. If you need to change this appointment for any reason, please contact us to let us know.

Although your scheduled study visits have now been completed, the study is planned to be ongoing for another [insert # of months] months. After that, we expect it will take about 3-6 months to have the results of the study available to share with all study participants. In order for us to share this information with you, we need to be able to keep in touch with you. Therefore we ask you to please inform us if you move to a new home, change your phone number, or have any other new details that would help us keep in touch with you. Give contact card.

As you know, [insert clinic/project name] is involved in many different types of research studies. We would like to be able to contact you in the future about other studies that you may be eligible for. Are you willing to give us your permission to do that? Record response on study exit worksheet; if permission is granted, explain that information recorded on the participant's locator form would be used for this purpose and enter participant on future contact permission log.

- *If applicable, reinforce plans to determine pregnancy outcome.*
- *If applicable, reinforce plans for AE follow-up.*

Lastly, we would like to give you some information on places where you can go for different types of services now that you will not be coming here for regular study visits: Give referral sheet

- *For HIV counseling and testing*
- *For family planning and other reproductive health care*
- *For other types of health care*
- *Other*

Please feel free to contact us if you have any questions about the study that we have not answered today, or if you encounter any problems related to your participation in the study. Once again, we sincerely thank you for your contributions to the study and we look forward to sharing the results with you when they become available.

Section Appendix 6-5
Sample Future Study Contact Permission Log

Participants Willing to Be Contacted for Future Studies By Participant Name

No.	Name	Date of Contact Approval	Method of Contact Preferred