Section 5. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up in MTN-011. Examples of visit checklists detailing the protocol-specified procedures and data collection forms that must be completed at MTN-011 study visits are available on the MTN-011 Study Implementation webpage: http://www.mtnstopshiv.org/node/4525.

5.1 Study Follow-up Plan and Participant Retention Targets

After enrollment, couples in Group 1 (Single Dose/BAT Cohort) will be in MTN-011 follow-up for approximately 7-55 weeks. Couples in Group 2 (Multiple Dose Cohort) will be in MTN-011 follow-up for approximately 14-34 weeks. A retention rate of 100% is targeted across sites. Further information on retention definitions and procedures for MTN-011 is provided in Section 6 of this manual.

Once accrual is complete for a specific matched-pair visit set, (20 evaluable couples per set) subsequent enrollments will be closed for that set and potential participants will only be allowed to enroll in those matched-pair visit sets with remaining accrual slots. Table 5-1 outlines the study visits required for Group 1 matched-pair sets. Table 5-2 outlines the study visits required for Group 2 matched-pair sets.

Table 5-1
Required Follow-up Visits for Group 1 Matched-Pair Sets

Matched-Pair Set	Required Visits
-1 hr	Screening, Enrollment, 3a, 3b, 4a, 4b
-24 hrs	Screening, Enrollment, 5a, 5b, 6a, 6b
BAT (Gel -1hr/Coitus/Gel +1hr)	Screening, Enrollment, 3a, 3b, 7a, 7b

Note: Once a couple completes 1 matched pair-visit set, they may continue to enroll in another matched pair set, provided additional matched pair sets are open to accrual. They will not need to repeat the Screening and Enrollment Visits, provided they are still within allowable visit windows

Table 5-2
Required Follow-up Visits for Group 2 Matched-Pair Sets

Matched-Pair Set	Required Visits
-1 hr	Screening, Enrollment, 3a, 3b, 4, 5
-72 hrs	Screening, Enrollment, 7a, 7b, 8, 9

Note: Once a couple completes 1 matched pair-visit set, they may continue to enroll in another matched pair set, provided additional matched pair sets are open to accrual. They will not need to

repeat the Screening and Enrollment Visits, provided they are still within allowable visit windows. In addition, Group 2 Visit 6 is not required if a couple is only completing Matched-Pair Set -72 hours, because the Enrollment Visit will serve as a replacement for Visit 6.

5.2 Types of Follow-up Visits

Scheduled Visits are those visits required per protocol. All scheduled visits are pre-assigned a visit code for purposes of data management, per Section 10 of this manual. In Group 1, female participants will have 12 scheduled follow-up visits (including enrollment visit); their male partners will accompany them for 5 of these visits. See Figure 5.1 for a MTN-011 visit summary for Group 1.

In Group 2, female participants will have 10 scheduled follow-up visits (including enrollment visit); their male partners will accompany them for 4 of these visits. See Figure 5.2 for a MTN-011 visit summary for Group 2.

If a couple is enrolling in one matched pair visit set, they will have 5 scheduled follow-up visits (including enrollment).

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 (see protocol Section 7.7). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 10 of this manual.

5.3 Follow-up Visit Scheduling

5.3.1 Target Visit Dates and Visit Windows

Target visit days and windows for MTN-011 are based on expected female participants' menses, time needed to heal from biopsies and tissue collection, and adequate gel washout time periods. Visit windows have been extended in Protocol Version 2.0 of the protocol to allow for greater scheduling flexibility. For MTN-011, the confirmation and final sign-off of the eligibility checklist (for both the female and male participants) per site SOPs is the effective point of enrollment of the couple and enrollment is considered Day 0.

Enrolled participants in Group 1 will have the following visits in MTN-011:

Figure 5.1: MTN-011 Scheduled Visits (Group 1)

Group 1: Single Dose/BAT Cohort				
Gel	**Visit**	**Visit Name**	**Targeted visit schedule**	**Coitus**
	1 ♂♀	Screening		
	2a ♂♀	Enrollment/ No Gel/ Coitus	To occur ~2-12 days after the final day of the female's last period*	X
	2b♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur ~3-90 days after visit 2b	X
	3b♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	
	4a ♀	Gel -1/No Coitus	To occur after a mininum10-day wash-out period, but not more than 56 days following the previously scheduled visit	
	4b ♀	Sampling	To occur at similar time point relative to visit 3b	
-24 hr	5a ♂♀	Gel -24/Coitus	To occur after a minimum 10-day wash-out period, but not more than 90 days following the previously scheduled visit	X
	5b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	
	6a ♀	Gel -24/No Coitus	To occur after a minimum 10-day wash-out period, but not more than 56 days following the previously scheduled visit	
	6b ♀	Sampling	To occur at similar time point relative to visit 5b	
BAT	7a ♂♀	BAT: Gel -1/Coitus/ Gel +1	To occur after a minimum 10-day wash-out period, but not more than 90 days following the previously scheduled visit	X
	7b/ Final ♂♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	

♀= female ♂= male

*If a participant is amenorrheic, this enrollment visit should be scheduled any time after the laboratory results from the Screening Visit are available and within the 30 day screening window.

** Blood and pelvic specimens will be collected approximately 2 hours after coitus; however samples will ideally be collected within a 1-3 hour window. If sample collection cannot occur within this window, sites may still collect specimens but contact the MTN-011 management team for guidance. In general, if the specimens are collected earlier than 1 hour or later than 4 hours after coitus, sites should still collect the samples but complete a protocol deviation form.

Enrolled participants in Group 2 will have the following visits in MTN-011:

Figure 5.2: MTN-011 Scheduled Visits (Group 2)
Group 2: Multiple Dose Cohort

Gel	Visit	Visit Name	Targeted visit schedule	Coitus
	1 ♂♀	Screening		
	2 ♀	Enrollment- Provision of Study Product	To occur approx. 2-12 days following the final day of the female participant's period*	
-1 hr	3a ♂♀	Gel -1/Coitus	To occur 6 days after Visit 2	X
	3b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	
	4 ♀	Provision of Study Product	To occur after a minimum 20 day washout period, but not more than 56 days following the previously scheduled visit	
	5 ♀	Sampling	To occur at similar time point relative to Visit 3b	
-72 hr	6 ♀	Provision of Study Product	To occur after a minimum 20 day washout period, but not more than 90 days following the previously scheduled visit	
	7a ♂♀	Gel -72/Coitus	To occur 9 days after Visit 6; participants to be counseled to insert last dose of gel approximately 72 hours prior to visit	X
	7b ♀	Post-Coital Sampling	To occur ~2 hrs after coitus**	
	8 ♀	Provision of Study Product	To occur after a minimum 20 day washout period, but not more than 56 days following the previously scheduled visit	
	9 ♂♀	Sampling/Final Visit	To occur at similar time point relative to Visit 7b; participants to be counseled to insert last dose of gel approximately 72 hours prior to visit	

*If a participant is amenorrheic, this enrollment visit should be scheduled any time after the laboratory results from the Screening Visit are available and within the 30 day screening window.
** Blood and pelvic specimens will be collected approximately 2 hours after coitus; however samples will ideally be collected within a 1-3 hour window. If sample collection cannot occur within this window, sites may still collect specimens but contact the MTN-011 management team for guidance. In general, if the specimens are collected earlier than 1 hour or later than 4 hours after coitus, sites should still collect the samples but complete a protocol deviation form.

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. Acknowledging that it will not always be possible to complete study visits on the targeted date, visits may occur within specific windows around target dates. Visit windows for MTN-011 differ from visit to visit and across study groups; a complete listing of visit windows is available in Section 10 of this manual.

Due to lengthy visit windows, if a couple returns for a study visit more than 42 days past their last attended clinic visit, both the female and male participant must be tested for

HIV, GC/CT, and Syphilis. Negative results for these tests must be obtained prior to dispensing gel and continuing with study procedures.

As MTN-011 is a pharmacokinetic and pharmacodynamics study, and every effort should be made to schedule participants within the timeframes as specified above. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the visit schedule.

5.3.2 Visits Conducted Over Multiple Days: "Split Visits"

Split visits will not be allowed in MTN-011. All procedures specified by the protocol to be performed at a given visit should be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day, contact the management team for further guidance. For example, if a couple fails to complete coitus (ejaculation into the vagina), the IoR/designee should consult the management team for procedure completion guidance. Visit procedures, such as specimen collection, may be omitted at the discretion of the management team and protocol chair. See section 5.10 for more details.

5.3.3 Missed Visits

For participants who do not complete any part of a scheduled visit within the visit window, the visit will be considered "missed" and a Missed Visit case report form will be completed for the female participant to document the missed visit. If the missed visit is one where the Male Practices Questionnaire is required, the Male Practices CRF must also be completed with Item 1 marked "no." Section 10 gives detailed information regarding the completion of the Missed Visit form.

5.4 Follow-up Visit Locations

All visits will be conducted at the site clinics. No study specific assessments may be completed off-site. Participants will engage in coitus at the hotel only. Site staff may offer the hotel either the night before or night following the scheduled sampling visits, based on hotel policies and site/participant convenience.

5.5 Study Product Supply/Dispensing during Follow-up

For Group 1 and Group 2, the doses that will be administered in the clinic will be dispensed on the day of the clinic visits. Doses that are to be self-administered at the hotel just prior to coitus, will be dispensed on that day at the clinic.

Group 1 Participants will be supplied with study gel applicators as follows:

Visit	# of Doses	Location of Use
3a	1	Hotel
4a	1	Clinic
5a	1	Clinic
6a	1	Clinic
7a	2	Both doses used at hotel

Group 2 Participants will be supplied with study gel applicators as follows:

Visit	# of Doses	Location of Use
2	7*	First dose in clinic. 5 daily doses at home.
3a	1	Hotel
4	7*	First dose in clinic. 5 daily doses at home.
5	1	Clinic
6	8*	First dose in clinic. 6 daily doses at home.
8	8*	First dose in clinic. 6 daily doses at home.

* Female participants will be dispensed one extra dose for home use, in case an applicator becomes unusable for any reason; however participants will be counseled to only use 5 applicators following visits 2 and 4; and 6 applicators following visits 6 and 8.

Product replacement will occur in the event of lost or damaged product that must be replaced. Additionally, if the female participant fails to administer the required number of doses during a study period (Group 1, one dose; Group 2, minimum of 5 doses), the site should consult the PSRT for guidance on rescheduling the participant to return to the clinic after a minimum washout period (Group 1, 10 days; Group 2, 20 days) and providing the participant with additional product. For complete details of study product replacement during follow-up please see Section 7 of this manual.

At follow-up visits, study staff will collect all unused and used study product (if any). Site staff will determine if the participant remains eligible for continued study product use per protocol specifications. Protocol Section 9 lists conditions under which participants should be discontinued from study product use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

Section 7 of this Study-Specific Procedures Manual contains detailed information on site clinic staff procedures for the dispensation of study product, as well as the return of used and unused study products.

5.6 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7 and Appendix I. Further operational guidance on completing protocol-specific follow-up procedures is incorporated into the visit checklists located on the MTN-011 Study Implementation Materials webpage: http://www.mtnstopshiv.org/node/4525.

5.7 Assessment of continued monogamy

Male and female participants will be assessed for continued monogamy at follow-up visits per protocol Appendix I. They will also be assessed for continued monogamy

when re-enrolling in the alternate study group or re-enrolling in a matched-pair set. If either the male or female partner self-report non-monogamy during follow-up, the couple will be terminated from the study. For confidentiality reasons, staff cannot inform the other partner of non-monogamy. It is suggested that sites come up with a standard way to explain discontinuation to study participants if this should occur. Documentation of assessment and reports of non-monogamy should be detailed in the participants' study records.

5.8 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who become pregnant after enrollment will be permanently discontinued from study product and they, along with their participating partner, will be terminated from the study. Participants in Group 2 will be instructed to return study product. Participants who are pregnant at the termination visit 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). Pregnant participants should be offered enrollment into MTN-016 if their study site is participating in that protocol.

5.9 Modified Follow-up Procedures for Participants Who Become Infected with HIV or STIs

Participants who become infected with an STI will receive treatment or be referred for treatment. Participants who become infected with HIV after enrollment will be counseled and referred for available sources of medical and psychosocial care and support. Female participants will be permanently discontinued from study product and they, along with their participating partner, will be terminated from the study. Participants in Group 2 will be instructed to return study product. HIV RNA and HIV drug resistance testing will be done on those participants who became infected with HIV and results will be provided when they become available. See section 9 for additional details.

5.9.1 Modified Follow-up Procedures for Participants Who Do Not Complete Coitus or Otherwise Do Not Adhere to the Study Protocol

If the female participant fails to administer the minimum number of doses during a study dosing period (Group 1: a single dose, Group 2: five doses), or if the female or male participant is unable to complete a clinic visit, or if coitus is not completed (when applicable) study procedures are to be modified as follows:

- Samples for PK, PD and biomarkers are to be omitted
- Behavioral assessments are to be omitted
- Pelvic exam and related procedures may be omitted, unless required for AE follow-up
- All other safety evaluations are to be omitted, unless required for AE follow-up
- Provision of study product and related procedures are to be conducted, if indicated
- Coitus and coital related procedures are to be omitted, when applicable

The site should consult the PSRT to determine if the couple should be rescheduled for the study visit and/or provided with additional study product if applicable; however if any study product was administered, a minimum washout period of 10-days is required for Group 1 and 20-days for Group 2.

5.11 Follow-up Procedures for Participants who Permanently Discontinue Study Product

If a participant, or their partner, permanently discontinues gel use, both individuals will be terminated from the study and female participants in Group 2 will be instructed to return any remaining unused study gel.

5.12 Follow-up Procedures for Participants who Withdraw

Participants can end their participation in the study at any time. If participants alert the site staff that they would like to end their participation, staff should ask if they would agree to complete a final visit (Group 1 Visit 7b, Group 2 Visit 9). Sites must also contact the MTN-011 Management Team requesting guidance on whether pK sampling should be conducted at this final visit. Details related to withdrawing consent should be documented in the chart notes.

If the couple is willing, site staff should conduct final visit procedures and complete all required CRFs for this visit, as listed in SSP Section 10.3.6. If the couple is not willing to complete one final study visit, site staff should complete the following CRFs: Termination (for both male and female), and End of Study Inventory (female only). Other forms may be required depending on their group assignment and whether product was returned; SCHARP will provide additional guidance as needed. When completing the Termination form, mark item 2c "participant refused further participation, specify" as the reason for termination. As with anytime a participant exits the study, be sure to review all completed log CRFs and make appropriate updates (e.g. Adverse Experience Log form and Concomitant Medications Log form).

A couple may withdraw from the study and later request to return and continue with study participation. If such cases arise, study staff are advised to contact the MTN-011 Management Team for additional guidance on how to manage various aspects of protocol implementation and data collection as the couple resumes participation in the study.

5.13 Product Use Instructions and Adherence Counseling

At visits when gel is dispensed, participants in Group 2 will receive detailed instructions for daily use of gel, followed by adherence counseling. At Visit 2 (Enrollment Visit), the female participants will insert the first dose in the clinic.

Participants will be instructed to insert one dose (the entire contents of one applicator) at approximately the same time every day. Female participants in both groups will be counseled to abstain from sex (oral, anal, and penile/vaginal) and other vaginal practices (masturbation, douching, etc.) 72 hours prior to each follow-up visit. Group 2 female participants will also be counseled to abstain from sex and vaginal practices during at-home gel use. Male participants will be counseled to abstain from sex (oral, anal, and penile/vaginal) and other penile practices (masturbation, application of lubricants/spermicides, etc.) 72 hours prior to each follow-up visit. Group 2 male participants will also be counseled to abstain from sex during partners' at-home gel use period.

In additional to adherence counseling that will occur in the clinic, female participants will be contacted two times during each home dosing phases, once at the beginning of the home dosing phase and once towards the end, to remind them to insert their study gel.

See Sections 8 and 13 for more details on product use instructions.

Adequate time should be taken to thoroughly explain the product use instructions and answer any questions the participant may have; any questions or concerns raised by the participant should be documented in study records so this information is easily available for reference at follow-up contacts.

5.14 Prohibited Practices

If a participant reports a prohibited practice as, as listed above and in protocol section 6.9, the continuation of the study visit procedures will be performed at IoR discretion. The prohibited practice should be thoroughly documented in chart notes. In addition, the prohibited practice should be noted on the comments section of the Pharmacokinetics CRF.

Although couples should not be encouraged to have sex (or any of the prohibited behaviors) 72 hours prior to certain visits, should this situation arise, it must be managed for future paired visits and documented. If a couple reports having had sex within the 3 days prior to Group 1 Visits 3a, 5a or Group 2 Visits 3a, 7a they should be instructed by study staff to also have sex prior to their next visit at approximately the same time of day. For example, if the couple has sex at the hotel the night before their scheduled Group 1, 3a visit, they should be instructed to have sex the night before Visit 4a at approximately the same time. In such cases, site staff must record the date and time of the prohibited sex act, along with any other pertinent details, on the comments line of the Pharmacokinetics CRF. Questions related to this occurrence should be directed to the MTN-011 management team.

5.15 Visit Checklists

The visit checklists (located at: http://www.mtnstopshiv.org/node/4525) are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. For example, chart notes may be required to:

- Explain why procedures in addition to those listed on a checklist were performed
- Explain why procedures listed on a checklist were not performed
- Document procedures performed at interim visits
- Document the content of counseling sessions and/or other in-depth discussions with participants (e.g., related to adherence to protocol requirements)

See Section 3 of this manual for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If information is written on the front and back of the checklist, enter the PTID and visit date on both sides.

- For interim visits, enter the visit code in the top section of the checklist.

- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., "done by {name}" or "done by lab staff."

- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item.

- If a procedure listed on the checklist is not performed, enter "ND" for "not done" or "NA" for "not applicable" beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

5.15.1 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN CORE (FHI 360), site staff may modify the checklists included in this section to maximize the efficiency of site-specific study operations. Sites may alter the sequence of procedures to suit local staffing and logistical requirements, with the following exceptions:

- Informed consent for screening and enrollment must be obtained before any screening procedures are performed.

- On the day of enrollment, provision of gel must take place **after** administration of the CASI Questionnaires, collection of blood for plasma archive, and final confirmation of eligibility.

- At visits when study product is dispensed, gel must be provided after clinical and behavioral assessments to determine if participant is eligible to continue gel use.