5 Introduction

This section provides information on requirements for study procedures in MTN-034, including screening, enrollment and participant follow-up visits.

5.1 Visit Location

Given the nature of the study procedures required to be performed during the MTN-034 study, all visit procedures are expected to be completed at the study clinic or by phone (for designated contacts one week after each product initiation period begins).

5.2 Eligibility Determination and SOP

It is the responsibility of each 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. Each study site

must establish a SOP that describes how site staff will fulfill the responsibility of determining participant eligibility. This Participant Eligibility Determination SOP, at a minimum, should contain the following elements:

- Eligibility determination procedures, including:
    - Eligibility assessment during the visit the Screening and Enrollment Visits
    - Post-screening visit eligibility assessment and confirmation procedures (i.e., review of laboratory results)
    - Final confirmation and sign-off procedures prior to enrollment
    - Documentation of each eligibility criteria (met or not met)
- Ethical and human subjects' considerations
- Staff responsibilities for all the above (direct and supervisory)
- QC/QA procedures (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 the MTN-034 Management Team (mtn034mgmt@mtnstopshiv.org).

5.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-034. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3; and required screening procedures are listed in Protocol Section 7.2.

In addition to the assessment of eligibility, informed consent/assent and parental/guardian permission should be reviewed to ensure that the participant and her parent/guardian clearly understands all information and is willing/permitted to participate in the study. Review of the informed assent and consent must be documented in the participant's study files (or using the Informed Consent Coversheet, if preferred).

All protocol-specified screening procedures must take place no more than 70 days prior to the Enrollment Visit. This window begins the day written parental/guardian permission and/or participant informed consent/assent is obtained. If participant assent occurs on a different day then parent/guardian permission, the screening window will begin with whichever is obtained first (e.g. if the potential participant signs the informed assent form, prior to her parent/guardian providing written permission, the 70-day window begins the day the informed assent form was signed).

The term "screening attempt" is defined as "each time the participant provides written informed consent/assent for participation in the study." If all screening and enrollment procedures are not completed within the allowable timeframe (i.e. 70 days) after obtaining written informed consent, one additional screening attempt will be allowed, per the discretion of the IoR or designee. The participant must repeat the entire screening process, beginning with the informed consent process. A new PTID will not be assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the participant successfully enroll in the study.

Per Protocol Section 7.2, multiple visits (as part of the same screening attempt) may be conducted if needed to complete all required procedures.

5.3.1 Screening Visit Procedures

Required screening procedures are reflected in the sample Visit Checklists available on the MTN-034 webpage. After provision of written informed consent/assent, participants will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Further details on PTID assignment, structure, and related information are included in SSP Section 12.

Administrative procedures include:

- Collection of locator and demographic information
- Reimbursement provision
- If presumptively eligible, scheduling their enrollment visit

Behavioral eligibility criteria, based on self-report, should be evaluated using the Screening Behavioral Eligibility Worksheet provided on the MTN-034 webpage. It is suggested that staff administer this questionnaire early in the visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined to be ineligible due to behavioral criteria. To maintain consistency across sites and participants, questions on this worksheet will be asked verbatim and participant responses should be recorded directly on the worksheet.

Clinical Screening Visit procedures, further described in detail in SSP Section 7, include:

- Collection of medical and menstrual history (as per protocol, she must be post-menarche); assessing concomitant medications; and conducting a physical and pelvic examination.
- Evaluation of the use of prohibited medications and practices, assessing STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Provision of HIV pre/post-test and risk-reduction counseling, contraception, and study approved condoms.
- Disclosure of all available test results to the participant, as well as treatment or referrals for UTI/RTI/STIs if indicated.

Per Protocol inclusion criteria #9 (Protocol Section 5.2), a participant is required to use the same effective contraceptive method for at least 2 months prior to enrollment. The site may schedule enrollment after confirming her history of using a reliable hormonal method or following provision of an acceptable method of contraception (IUD and other hormonal methods). Eligible participants must also have a history of sexual intercourse (e.g. penile-vaginal intercourse), defined as at least one episode in her lifetime.

The HIV testing algorithm for screening is included in Appendix II of the Protocol.

Details regarding laboratory tests and sample collection at screening are provided in SSP Section 9. In summary, all participants will:

- Receive testing for HIV, pregnancy, Hepatitis B surface antigen, STIs (Syphilis, Gonorrhea, Chlamydia and Trichomonas), CBC with platelets, and serum creatinine (along with calculated creatinine clearance).
- If indicated, have a wet prep mount for candidiasis and/or BV, vaginal pH test, and urine dipstick urinalysis/ urine culture.

Between screening and enrollment, appropriately delegated site staff should review lab results and other eligibility criteria. If the participant meets eligibility criteria at the end of the Screening Visit, she should be scheduled for her Enrollment Visit, making sure the enrollment visit takes place within the allowable 70-day time frame. Participants should be provided with study informational material, clinic contact information, and instructions to contact the clinic with any questions as needed prior to her scheduled Enrollment Visit. The participant should also be reminded to refrain from engaging in prohibited study practices beginning 72 hours prior to her enrollment visit.

5.3.2 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 screening and enrollment logs. These logs may be maintained separately or combined into one document. Also, in accordance with the MTN Manual of Operational Procedures (MOP) Section 13.1, participants' initials/names do not need to be recorded on screening and enrollment logs if it presents a potential threat to participant confidentiality. For the purposes of MTN-

034, the template Screening and Enrollment log will not include initials/names, and a separate PTID Linkage Log will serve as a link between a participant's name and PTID. The PTID Linkage Log must be stored in a secure location. Further details on the PTID Linkage Log is included in SSP Section 12.

A sample Screening and Enrollment Log is available on the MTN-034 website. Study sites are encouraged to reference the eligibility codes listed at the bottom of the log when recording all reasons for screening failure/discontinuation.

5.3.3 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. If the participant is found to be ineligible at the beginning of the Screening Visit, sites may choose to continue with clinical and laboratory evaluations as a service to the participant, per their site SOPs. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure the well-being of the participant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination.

For all screened-out participants, the following documentation should be in place:

- Completed informed consent/assent and parental/guardian permission form
- Reason(s) for ineligibility, with date of determination
- Completed Eligibility Criteria CRF
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- All source documentation completed up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on Visit Checklists)
- Completed entry on the Screening and Enrollment Log (updated with date of discontinuation of screening and reason for screen failure)

Reasons for screen failures should be consistent between the Screening and Enrollment Log and the Eligibility Criteria CRF. Regarding eligibility criteria categorization for HIV-related screen-outs:

- A participant with at least 1 positive HIV rapid test, no matter the outcome should be deemed ineligible per Exclusion Criteria 2 (E-2): At Screening or Enrollment, has a positive HIV test.
- A participant confirmed HIV-infected (i.e. has 2 positive rapids or discordant rapids with a positive confirmation) should be deemed ineligible per E-2 and Inclusion Criteria 6 (I-6): HIV-uninfected based on testing performed at Screening and Enrollment.

Screening HIV Rapid Test Results	Final HIV Diagnosis (confirmation)	Eligibility Criteria	
		I-6	E-2
Dual Negative	NA	No	No
Discordant	Infected	Yes	Yes
	Uninfected	No	Yes
Dual Positive	NA	Yes	Yes

5.4 Enrollment Visit

Enrollment procedures are specified in Protocol Section 7.3 and reflected in the sample Enrollment Visit Checklist available on the MTN-034 study website. A participant is considered enrolled in the study when she is randomized via the MTN-034 Medidata Rave clinical database. All baseline samples and examinations must be collected/completed before a participant is randomized and study

product is administered. Further information on methods and materials for study arm assignment is provided in the SSP Section 12 Data Collection.

5.4.1 Enrollment Visit Procedures

The Enrollment Visit serves as the baseline visit for all enrolled study participants. An accurate assessment of baseline conditions must be documented, and eligibility must be confirmed, on the day of Enrollment. All procedures for this visit must be conducted on the same day and cannot be split across multiple days.

The only exception to this will be for sites that are required to administer a separate informed consent/assent (IC) form at the Enrollment visit per local IRB/EC regulations. For those sites, the IC for Enrollment may be performed on the first day of the split visit. All other protocol-specified visit procedures required at Enrollment must be completed at a single visit as close as possible to IC provision (i.e. the date in which the participant signed/dated/marked the Enrollment IC form). If the participant cannot complete enrollment within her Screening to Enrollment window, she should be considered a screen fail.

In brief, procedures occurring before and after randomization are noted below.

5.4.1.1 Procedures Completed PRIOR to Randomization

The participant should undergo the following procedures before randomization:

- Confirm the informed consent/assent and parental/guardian permission forms, as applicable, have been signed and dated and the participant remains willing and able to participate in the study.
- Confirm the 70-day screening window has not been exceeded.
- Update and reconfirm adequacy of locator information.
- Confirm behavioral eligibility criteria by administering the Enrollment Behavioral Eligibility Worksheet.
- Review and update the participant's medical and menstrual history that was first collected at the Screening Visit.
- Evaluate participant's use of prohibited vaginal practices, products and medications and assess for STI/RTI/UTIs or reproductive tract signs/symptoms.
- Collect urine for pregnancy testing.
- Collect blood for HSV-2 antibody, HIV testing and plasma archive, and, if indicated, for CBC with platelets and creatinine clearance.
    - Note: For sites not conducting finger stick HIV rapids: to reduce participant burden, sites should consider collecting plasma archive and HIV samples as part of a single blood draw.
- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling, including offer of condoms.
- Provide contraceptive counseling and discussion of pregnancy/breastfeeding history and future pregnancy intentions.
    - Note: If a participant elects to change her contraceptive method at the enrollment visit, she should not proceed to enrollment at that visit as she must use the new contraceptive method for at least two months prior to enrollment. It is recommended that sites use the time period from screening to enrollment to counsel potential participants to avoid this scenario.
- For those who have not received prior vaccination (and those that test negative for HBsAg), offer immunization against HBV and HPV, as applicable and if available per local standard of care. Hepatitis B and HPV vaccinations are not required to be eligible for enrollment in the study. All vaccinations should be recorded on the Concomitant Medications Log CRF. Each injection should be recorded as a separate entry. Participants who decline vaccination at

enrollment should continue to be offered vaccination throughout follow-up and, if they later accept vaccination, may initiate the vaccine series at any time.

- Provide protocol adherence counseling, including study product use instructions.
    - Note: This may also be conducted after randomization, but it could be helpful to provide the participant with more information about the study product prior to her final decision to enroll in the study.
- If indicated, conduct a physical exam to confirm the participant is in good general health.
- Conduct pelvic exam and collect appropriate samples in the sequence shown on the Pelvic Exam checklist.
- Disclose all participant's available test results and, if indicated, provide treatment or referrals for STI/RTI/UTIs.
- Once it is clear that the participant is likely to be eligible, but prior to her knowing what study product she is assigned to, complete the Baseline ACASI Behavioral Assessment and Product Preference/Acceptability Assessment.
    - Note, this may be done after randomization, for purposes of visit flow, as long as the participant completes ACASI prior to her knowledge about first product assignment.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to study product sequence, at which point she will be considered officially enrolled in the study. Designated staff will document the status of each eligibility criterion on the Eligibility Checklist. The Eligibility Checklist should be started on the day of enrollment and the site IoR (or designee) and a second staff member should sign and date the Eligibility Checklist to confirm eligibility status prior to being enrolled. All staff members who are responsible for signing off on the Eligibility Checklist should be clearly delegated per the DoD Log and listed as sub-investigators on the FDA Form 1572. Only staff delegated the responsibility of eligibility determination per the site DoD Log may complete the Eligibility Confirmation signature line; note that a second staff member also delegated the responsibility of eligibility determination must complete the Eligibility Verification signature box.

If the participant is found ineligible before the enrollment visit, the Eligibility Checklist does not need to be started. If a participant is found to be ineligible at the enrollment visit and the checklist has been partially completed, there is no need to continue filling out the checklist past the point when ineligibility is determined.

5.4.1.2 Procedures Completed AFTER Randomization

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to a study product sequence, at which point she will be considered officially enrolled in the study. Participants will additionally be randomized at this time to be considered for a serial In-depth Interview (SIDI). If a participant is invited for an IDI, clinic staff should confirm verbally the participant's willingness to participant in an IDI and be audio recorded. Document the IDI selection outcome on the Qualitative Participation Log (QPL) and the Enrollment CRF. See SSP Section 12 Data Collection and Section 11 Behavior Procedures for more information on completing study product sequence and IDI randomization.

After randomization, the following procedures should be completed:

- Provide the applicable enrollment session Product Adherence Counseling (PrEP or Ring) to discuss expectations and strategies for product adherence with the participants.
- Prescribe study product (by the IoR or authorized clinician), obtain product from the site pharmacy, review the product use instructions and answer any questions that the participant may have.
- All study participants will complete their first product use at the study clinic during their Enrollment Visit. Study staff should perform a digital exam to verify ring placement for Vaginal Ring (VR) users and observe ingestion of the first study tablet for Truvada users and document on the applicable CRFs.

- The rationale for this is to help ensure participant understanding, comfort, and confidence with proper product use from the very beginning of study participation. Any questions or concerns that arise in the context of first product use can be addressed by study staff before the participant is required to use study product on her own. For further detailed guidance on first product use, refer to SSP section 10.5.

- After the participant completes the first product use, study staff should de-brief with the participant on the first product use experience. If the participant has any questions or issues, these should be documented so the information is easily available for reference at study follow-up visits.
- Schedule follow-up visit for the one-week post-study product initiation Phone Contact (Visit 3) and provide reimbursement.

5.5 Follow-up Visits

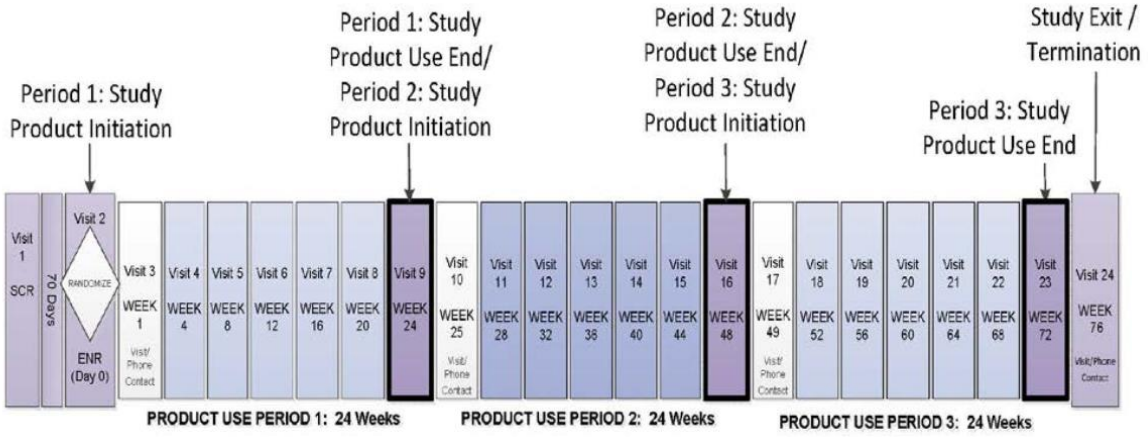
Throughout the study follow-up period, two types of follow-up visits may be conducted:

Scheduled visits are those visits required per protocol. The protocol specifies that follow-up visits are targeted to occur monthly (every 4 weeks). Although the structure of the visit windows may allow for more than 30 days between monthly visits, site staff should be mindful of product resupply needs. This is especially important for participants continuing with the oral tablets to ensure they have no lapse in supply to cause missed doses. If a participant is scheduled to initiate VR use during her menses, she may choose to delay study product initiation until the completion of menses.

All participants will also be scheduled for a visit/phone contact which occurs approximately one week after study product initiation for all three product use periods (Visits 3, 10, and 17), as well as one week after the Week 72/Product Use End Visit (PUEV) (Visit 24). Required study procedures during these contacts are outlined in Protocol section 7.4.

Interim visits are those visits/contacts that take place, as needed, between scheduled visits. See SSP Section 12 for details on interim study visits and visit codes.

Figure 1: Study Visit Schedule



5.5.1 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Section 7-4 and Appendix I. Several additional clarifications of the procedural specifications are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures during follow-up is incorporated into the Sample Visit Checklists available on the MTN-034 website.

As a general guide, monthly visit procedures may include:

- Review/confirmation of locator information, visit scheduling and provision of reimbursement.
- HIV and urine pregnancy testing.
- Provision of HIV pre- and post-test counseling and modified HIV/STI risk reduction counseling, including offering condoms.
- Assessment/review of social harms and benefits.
- Contraception counseling and, if needed, provision of contraception.
- Medical/menstrual/medication history review including recording/updating any adverse events (AEs) and concomitant medications.
- Provision of all available test results; provide/refer for treatment for UTI/RTI/STIs and offer HPV and HBV vaccine series as needed.
- Provision of protocol adherence counseling.
    - Note: In the instance that a participant reports not adhering to protocol adherence requirements (i.e. she has had receptive intercourse within 3 days prior to the study visit), she should proceed with the visit but the deviation should be noted on sample collection documents and reported as a protocol deviation.
- Provision of product use adherence and drug level feedback disclosure counseling.
- Performing a physical exam and pelvic exam and testing for UTI/RTI/STIs or other clinical conditions.
- Collection and storage of blood and pelvic specimens for drug level testing/feedback/storage and safety and/or STI testing.
    - Note: Blood samples for DBS only need to be collected for participants who were taking Truvada during the previous month (assigned in period 1 or 2, or per choice during period 3). These samples are not relevant for participants who used either the VR or no product during the previous month.
- Collection of used rings for storage and future testing, or unused study tablets for destruction.
- Provision of new supply of study product (new vaginal ring insertion with digital exam to check placement (as needed); or a new bottle of tablets with first dose directly observed) and reminder to participants using tablets to wait to take their dose in the clinic on days when they have a follow up visit.
- Administration of behavioral assessments, including administering the ACASI and behavioral CRFs and conducting in-depth interviews and focus groups discussions as detailed in SSP section 11.
    - NOTE: the COVID-19 Behavioral Assessment (CBA) CRF should be administered as soon as possible following approval by the IRB/EC (if approval is required). This CRF will be administered a second time 3 or more months after the initial assessment for all participants (but no later than the Product Use End Visit).
- Detailed information on laboratory evaluations are described in SSP section 9.

Early termination/product use end visits will include a subset of procedures noted above; these are outlined in protocol section 7.4.3 and are included in the Visit 23/ PUEV Sample Visit Checklist.

While sites should aim to perform procedures in the order indicated in the approved site study visit checklists, it is acknowledged that this might not always be possible. If procedures are consistently listed out of order on the site study visit checklists, sites are encouraged to update their checklists and send to FHI 360 for review.

During Period 3 (choice period), participants may switch between using the Dapivirine ring and the Truvada tablets or choose neither as often as they desire. A Product Discontinuation log CRF must be completed in every instance a participant stops using either study product. Product change is at the participants' discretion; site staff should not prompt the participant on whether she would like to change methods. At the start of Period 3 and based on which methods chosen, site staff will provide applicable product use instructions and adherence counseling. Counseling should include a reminder of important key messages as well as address any questions she may have.

Site staff should also review with the participant the approximate amount of time that the study product takes to become effective after its started. For example, it is estimated that it takes between 1-3 weeks for Truvada to reach high levels of protection in the body. When used every day, Truvada can provide greater than 90% protection from HIV risk. Protection from the Dapivirine ring is highest with regular and consistent use. The ring does not offer protection if it is not used at all. In previous studies, among women who appeared to use the ring most or all the time, HIV risk was reduced by at least half, and in some cases, by 75% or more. It is important for participants to know that if the ring is worn most of the time, but not in place at the time of exposure to HIV (for example, if it is taken out before sex), then she may not be protected. In addition, participants should be informed that the ring does not protect against HIV during receptive anal intercourse. It is also important to remind all participants to use condoms to further protect them from HIV and acquisition of other STIs.

5.5.2 Visits Conducted Over Multiple Days: Split Visits Procedures

All procedures specified by the protocol to be performed at a follow-up visit, ideally, will be completed at a single visit on a single day. If all required follow-up procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on a separate day but within the visit window, if possible. When this happens, it is referred to as a “split visit.” Split visits are permitted for any type of follow-up visit in MTN-034.

If study visits must be split, note that:

- HIV pre- and post-test counseling and HIV testing should all occur on the same day.
- ACASI questionnaire and behavioral forms completion should occur on the same day.
- All PK specimens (blood and CVF for biomarkers) must be collected on the same day to avoid complicating interpretability of the data.

At a minimum, all the following procedures must be conducted during split or interrupted visits to dispense study product:

- AE assessment and reporting (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product).
- HIV testing, HIV pre- and post-test counseling and pregnancy testing.
- If applicable, collection of used rings or unused study tablets.

5.5.3 Missed Visits

If no procedures of a scheduled visit are conducted within the visit window, a Missed Visit CRF is completed. For this study, visit windows are contiguous, and as such no procedures are required to be made up at subsequent scheduled visits. In the event of a missed visit, an interim visit may be required to resupply rings/tablets and conduct associated safety assessments and counseling as needed (see minimum procedures required to dispense rings/tablets outlined in SSP Section 5.5.2 above).

5.5.4 Drug Level Adherence Feedback Results

Sites will receive PTID-specific reports with drug level feedback results as they are available from the following laboratory testing sites: FARMOVS for the VRs, and University of Cape Town (UCT) for the DBS samples. Reports will be in PDF format and include: the site name, PTID, Global Specimen ID (LDMS) for each sample tested, visit code when sample was collected, specimen collection date, specimen name, drug level (xx.x mg or xxxx fmol/punch), limits of quantification, testing lab name, and type of test performed.

Sites should counsel participants on these results at the next visit during the scheduled Product Adherence Counseling. Sites should plan to send one batch of VRs or DBSs per week to the respective testing labs. Shipping is expected to take 1-2 days, sites should contact the LC and respective testing labs in the event of shipment delays. The results should be available approximately 21 days from UCT and 14 days from FARMOVS following shipment receipt by the respective labs. Ideally sites should receive results no later than 2 days prior to the visit in which they will be provided in counseling as this will allow the site time to prepare the results for disclosure. If expected results are not available 3 days before a scheduled visit, the site should immediately contact mtn034dbsresults@mtnstopshiv.org (for DBS) or mtn034rdfeedback@mtnstopshiv.org (for residual VR). The MTN LC and testing labs will assist the site to determine the results' status.

Note: The COVID pandemic may make shipping impossible or unadvisable because of flight limitations. Discuss any potential shipping challenges or delays with the MTN LC or MTN-034 Management Team.

In preparation for the counseling sessions, clinicians will categorize the results into protection levels using the algorithm tool provided by SCHARP, available on the MTN-034 website. The site pharmacist will provide the clinicians with the ring lot load level to calculate the drug level result. Each drug level result will be categorized as 'low', 'medium' or 'high', with the applicable color coding (red, yellow and green, respectively), based on qualitative category cut-off points.

Information on the qualitative category cut-off points and ring load levels, as well as the translation from drug levels to the protection level categories can be found in the MTN-034 Drug Level Feedback Process Document available on the REACH website.

Designated site staff will transcribe both the drug level and the category of protection on the Adherence Counseling CRF completed at the visit in which the results were provided.

For more details regarding the drug level feedback process, refer to SSP Section 9 Laboratory Considerations, SSP Section 10 Counseling Considerations, and the MTN-034 Drug Level Feedback Process Guide available on the MTN-034 website.

5.6 Procedures for Participants Who Have a Positive Rapid HIV Test Result

In the event a participant has a positive rapid HIV test result(s), the following procedures must be done the same day of the reactive result is identified:

- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR
- CBC with platelets
- Blood creatinine for creatinine clearance
- Collection of PK and biomarker specimens
- Retrieve any study product in the participant's possession (within 24 hours of awareness).

5.6.1 Participants with a Positive Rapid HIV Test Who Are Confirmed as HIV-Uninfected

For participants who have a positive rapid HIV test result and are later confirmed HIV-uninfected per the algorithm in Protocol Appendix III, product use and all protocol-specified visit procedures may be resumed if desired by the participant.

Once product is resumed, clinic staff should inform pharmacy staff of the resumption in writing, using a Study Product Request Slip signed by an authorized prescriber (or a prescription if the participant has not previously been accepting product or is scheduled to change to a new product).

Clinic staff should also update the Product Hold Log CRF to document eligibility to resume product use. If the participant declines study product use in this case and has had a prescription completed, a Study Product Request Slip marked 'Resume' should still be sent to the pharmacy. On this same slip,

clinic staff will also mark 'decline,' to indicate that the participant is not accepting study product for use even though she is approved to resume product use.

Moving forward, sites must adhere to all guidance provided by the MTN LC for follow-up HIV testing plans for these participants (e.g. using alternate approved HIV rapid tests). In cases where an alternate HIV rapid kit is used, sites must have a system to alert testing personnel of this in advance. The HIV algorithm must be initiated whenever there is an HIV positive rapid test.

5.6.2 Procedures for Participants Who Become HIV-Infected

The following procedures must be done for participants whose HIV infection is confirmed per the algorithm in protocol Appendix III:

- **Permanently discontinue participant from study product.** Once the participant is identified as HIV-infected, complete a new Study Product Request Slip, if indicated (i.e. for participants who have ever had a prescription completed), to notify the Pharmacy (mark 'permanent discontinuation'), update the status for the item "Was the participant instructed to resume study product use?" in the Product Hold Log CRF (the one originally completed for the reactive HIV rapid test result) to indicate the participant was permanently discontinued, complete a Product Discontinuation Log CRF, and update the participant's final HIV status in the HIV Confirmatory Results CRF to reflect the participant's HIV-infected status. Study staff should not wait to inform the participant of her HIV-infected status to complete these items.
- Inform participant of her confirmed HIV-infection status. Counsel and refer her to local care and treatment services per site SOPs.
- **Plasma collection, CD4+ T cell count and HIV-1 RNA PCR** will be performed at the clinic visit immediately following confirmation, and every three months thereafter for the remaining follow-up period, or as indicated. Refer to the Seroconverter Schedule Tool (within the Visit Calendar Tool) available on the MTN-034 website.
- **HIV-1 genotyping** will be performed on the stored plasma closest to the time of confirmed HIV-1 infection. It may be performed at additional/alternate time points as requested by site IoR or at the discretion of the MTN LC.
- **Behavioral (including COVID-19 Behavioral Assessment), adherence, and product preference/acceptability assessments** will be performed at the clinic visit immediately following confirmation of an HIV-infection.
    - The COVID-19 Behavioral Assessment should not be administered in cases where the participant had already completed it twice, or if they had completed it within the past month. I.e., participants will only complete it if they have not yet completed the CBA CRF or if they only completed only 1 CBA CRF to date, and it was at least 1 month prior to date of confirmed positive HIV test.

* Note: if a participant misses her first monthly visit following seroconversion, contact the MTN-034 Management Team for guidance on the missed laboratory and behavioral procedures.

A participant identified as HIV-infected will be offered the option to continue follow-up visits per her original study schedule. For those who choose to remain in follow-up, the following procedures will be discontinued:

- HIV-1 testing, HIV pre- and post-test counseling.
    - Note: HIV/STI risk reduction counseling should continue and be modified to address primary and secondary infection prevention.
- Collection of PK and biomarkers specimens.
- Provision of study product, use instructions, product adherence and disclosure and protocol counseling.
- Administration of behavioral (including COVID-19 Behavioral Assessment), adherence, product acceptability/preference assessments.

The MTN-034/REACH HIV Confirmation and Seroconverter Guide provides an overview of the HIV confirmation testing protocol, follow-up procedures for seroconverters who remain in the study, and

study considerations for seroconverters. This guide is available on the MTN-034 study website and should be referenced upon an HIV rapid test result that is positive or indeterminate. Sites are encouraged to use a modified visit checklist for a participant who remains in follow-up to ensure only study procedures required for seroconverters are performed. A sample Seroconverter Follow-Up Visit Checklist is available on the MTN-034 study website.

5.7 Modified Procedures for Participants Who Become Pregnant

Pregnancy testing will be performed for all participants at scheduled visits. Testing will also be conducted, if indicated, at interim 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 per site SOPs.

The IoR/designee also will refer the participant to antenatal care available per site SOPs, however sites will not be responsible for paying for pregnancy-related care.

Participants who become both pregnant and infected with HIV will also be referred to prevention of mother-to-child transmission (PMTCT) services and will be offered expedited resistance testing at the MTN LC to provide information that may be useful for identifying optimal PMTCT regimens. Site staff should notify the PSRT promptly. HIV testing of participants' infants will be offered through the study if such testing is not otherwise available. All referrals and offers of additional testing available through the study will be documented in participants' study records.

Upon confirmation of a positive pregnancy test, the following study procedures are required (regardless if scheduled to occur):

- HIV -1 testing, HIV pre- and post-test counseling
- CBC with platelets
- Blood creatinine for creatinine clearance
- Collection of blood and pelvic specimens for PK and biomarkers
- Behavioral (including COVID-19 Behavioral Assessment), adherence, and product preference/acceptability assessments
    - The COVID-19 Behavioral Assessment should not be administered in cases where the participant had already completed it twice, or if they had completed it within the past month. I.e., participants will only complete it if they have not yet completed the CBA CRF or if they only completed only 1 CBA CRF to date, and it was at least 1 month prior to date of confirmed positive pregnancy test.
- Retrieve any study product in the participant's possession (within 24 hours of awareness).

The study site will make effort to contact participants and collect infant outcomes at approximately one year after delivery for those pregnancies that result in live birth. Information on infant outcomes one year after delivery should be documented in chart notes.

Participants who become pregnant during the study will temporarily hold study product and will not routinely be withdrawn from the study. Participants who become pregnant will be offered the option to continue follow-up visits with a modified study visit/procedure schedule until her originally scheduled study exit date. For those participants who choose to remain in follow-up, the following procedures will be discontinued:

- hCG urine test
- Provision of study VR(s) or study tablets, provision of product use instructions, and retrieval and collection of study VR(s) or study tablets
- Pelvic examination as well as associated procedures after 24 weeks of pregnancy, unless the participant indicates comfort with continuing vaginal procedures post 24 weeks
- Collection of PK and biomarker specimens
- Behavioral (including COVID-19 Behavioral Assessment), Adherence and product preference/acceptability assessments

- Provision of protocol adherence and product adherence disclosure counseling
- Provision or referral for HPV vaccine. If the vaccine series was initiated prior to pregnancy, scheduled doses may resume after the pregnancy outcome at clinician discretion.

A sample Pregnant Participant Follow-Up Visit Checklist is available on the MTN-034 study website.

For participants who become pregnant, a Pregnancy Report CRF must be completed to report the pregnancy. A Pregnancy History CRF must be completed only for the first reported pregnancy during the study. Participants who are pregnant at the Study Exit/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). A Pregnancy Outcome CRF must be completed to document the outcome of the pregnancy. Whenever possible, pregnancy outcomes should be collected from medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, outcomes may be based on participant report.

If a participant is pregnant, site staff should complete a Study Product Request Slip, marked "hold" and specify the reason. Clinic staff should complete the Product Hold Log CRF to document product hold and the date of the product hold initiation should be the date of the positive pregnancy test. Finally, site staff should complete a Pregnancy Case Worksheet for participants who become pregnant during study participation. This worksheet is available on the REACH study website.

The MTN-034/REACH Pregnant Participant Guide provides an overview of the follow-up procedures for a pregnant participant who remains in the study, and outlines study considerations for managing pregnant participants and pregnancy outcomes. This guide is available on the MTN-034 study website and should be referenced upon a positive pregnancy test result.

5.8 Modified Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

For this study, product use management may involve temporarily holding or permanently discontinuing either the vaginal ring or study tablet use for individual study participants, to protect their safety and well-being while in the study. A participant may be temporarily or permanently discontinued from one study product and be eligible to use the other product; however, if a participant is temporarily or permanently discontinued from either study product, she cannot choose to such product during the third/choice period.

Participants who either temporarily or permanently discontinue from one product use will not routinely be withdrawn from the study. Participants that discontinue study product will be encouraged to remain in the study, if they are willing, until their scheduled end-date. Every effort will be made to complete all protocol-specified follow-up visits, according to their original schedule, and modified procedures with these participants.

Additional guidance regarding procedures to be completed in the event of a temporary or permanent discontinuation are noted below. For conditions requiring temporary or permanent product discontinuations, see Protocol Section 9 and SSP Section 7.13.

5.8.1 Temporary Hold

If study product use is temporarily held, all other protocol-specified study procedures will continue except the following procedures:

- PK and biomarker specimens should be collected at the visit in which the hold is initiated (regardless if scheduled to occur or not). These samples, however, should not be collected at subsequent visits while the hold remains in place.

- Study product (vaginal ring or study tablets) will no longer be supplied to participants who have study product held. Associated product use instructions and protocol adherence counseling will also be discontinued.
- If data is available, product adherence disclosure counseling (e.g. PK or residual drug results) will continue to be provided to participants for the given study product use period. Subsequent counseling sessions that occur during the period of product hold should be discontinued.

If a participant resumes study product use, the above listed procedures should be resumed.

For participants who become pregnant, product use may be resumed 8 weeks following birth (provided the participant is not breastfeeding and in consultation with the PSRT) or loss of the pregnancy. For a pregnancy loss, the product restart timeline begins upon the date of the loss (i.e. bleeding, elective termination, etc.). A negative pregnancy test date should be used if the date of pregnancy loss is completely unknown.

Before resuming product, the participant must 1) confirm a negative pregnancy test performed by study staff, 2) not be breastfeeding, 3) be otherwise clinically eligible, 4) and be approved by site consultation with PSRT. A pelvic exam is required before resuming VR use to confirm the absence of any findings that would contraindicate resumption in the opinion of the IoR/designee.

5.8.2 Permanent Discontinuation

Participants who permanently discontinue study product use for one of the two study products for any reason (clinician-initiated or self-initiated) during the first or second study product use period may continue study participation by initiating the next study product use period (i.e., second or third) after consultation with the PSRT. Participants who permanently discontinue study product use for one of the two study products during the third product use period may continue study participation if they choose to use the other study product for the remainder of their study visits after consultation with the PSRT.

For example, a participant is assigned to sequence A, but is permanently discontinued from vaginal ring use in Period 1 due to an allergic reaction. The participant may proceed to and initiate Period 2 (use of the study tablets for 6 months) at visit 9 as per her originally scheduled visit calendar. During Period 3 she may only choose to use the study tablets or no product.

Alternatively, if she successfully completes Period 1, and initiates Period 2 but is permanently discontinued from use of Truvada due to a decreased creatinine clearance, she may proceed to and initiate Period 3, but may only choose to use the vaginal ring or no product.

Participants who permanently discontinue use of both products (e.g. are permanently discontinued for any reason during the first and second product use periods) will be considered terminated from the study as continued study participation would be of no added benefit. Participants will be asked to complete the procedures outlined in Protocol Section 7.4.3 (Product Use End/Early Termination Visit), if willing.

Participants who permanently discontinue study product use due to an AE must continue to be followed until resolution or stabilization of the AE is documented.

5.9 Participant Transfers

In the unlikely event that, during the course of the study, a participant leaves the area in which they enrolled in the study and re-locates to another area where the study is taking place, participant transfers may be allowed. 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. Detailed guidance on participant transfer procedures is outlined in the MTN MOP Section 13.2.4.

5.10 Voluntary Withdrawal/Early Termination

Participants may voluntarily withdraw from the study (withdraw consent) and terminate their study participation for any reason at any time. In these cases, site staff should ask the participant if she would be willing to complete one final study visit, which would count as her early termination visit. If the participant is willing, early termination procedures will be done per Protocol Section 7.4.3 (Visit 23/Week 72-PUEV). At the minimum, staff should:

- Perform a final HIV test.
- Complete the Study Termination CRF, mark "Withdrawal of Consent By Participant" and specify the reason the participant has refused further study participation.
- Record the reason(s) for the withdrawal in participants' study records.
- Update participant locator form.
- Ensure all referrals are provided to participant as needed
- Collect any VRs or tablet bottles still in the participant's possession and document returns on applicable forms and CRFs. Note: If study product is not returned within 5 business days of study termination, a protocol deviation should be reported.

The IoR may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, in consultation with the PRST. It is recommended that site IoRs use their discretion with regards to terminating participants who relocate and cannot transfer to another study site or can no longer come to the clinic, and are unlikely to resume study visits after counseling efforts and discussions with appropriate study staff.

All discussions, counseling, and decisions about early termination should be adequately documented in the participant's study records. Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.

Site teams are encouraged to review their Retention SOPs to make sure any site-specific procedures are in line with this guidance (e.g. that site teams may consider early termination as one option for participants who permanently relocate).

5.11 Resumption of Study Participation After Voluntary Withdrawal

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, per their original visit schedule. The resumption of study procedures and follow-up are subject to the IoR's discretion, pending PSRT consultation. If such cases arise, study staff are advised to contact the MTN-034 Management Team for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Participant's random assignment also will remain unchanged and she will continue product use per her random assignment.
- Prior to performing any study procedure, the participant and her parent/guardian (if applicable) must re-consent to document that she voluntarily rejoined the study. Site staff should thoroughly document in the participant's chart notes her resumption of study follow-up, and if applicable, study product use and all communication with the study management team and PSRT.
- An interval (since the last visit) medical and medication history should be taken and HIV and safety laboratory testing should be done as soon as the participant resumes study participation.
- A pelvic exam should be performed as soon as possible, and prior to re-instating vaginal ring use. Other clinically-indicated evaluations should be performed if the participant reports symptoms.

- After the above procedures are performed, the IoR or designee should include the results and findings of these procedures, and any other relevant participant history information, in a PSRT query form, and should submit the form to request PSRT consultation on resumption of product use. A copy of the final PSRT query form should be filed in the participant's study notebook.
- If resumption of study product use is approved by the PSRT, site clinic staff will communicate this decision to site pharmacy staff in writing. Resupply should be indicated on the Study Product Request Slip with a comment clearly stating that the participant has decided to rejoin the study and is clinically eligible to receive study product. If a participant has never previously accepted either study product but wants to initiate use, a prescription should be completed for this initial dispensation.

5.12 Product Use End Visit and Study Exit Visit

The final two required follow-up visits for MTN-034 are the Product Use End Visit (PUEV-Visit 23) and the scheduled study exit visit SEV)/termination (Visit 24).

- The PUEV serves as the planned end of product use for the 3rd choice period.
- The scheduled SEV serves as the final follow-up visit for all participants. The study termination date is to be approximately 4 weeks after PUEV. Therefore, a participant should not be terminated prior to the window opening of Visit 24 unless consent is withdrawn and/or the participant is terminated early from the study. As a reminder, the AE reporting period begins at the time of randomization and ends when the visit window closes for Visit 24.

The follow-up contact/scheduled SEV (Visit 24) may be scheduled as an in-clinic visit or as a phone call. During the participant's PUEV, site staff should discuss with the participant what procedures will be conducted during this visit/contact. Depending on results from labs collected during PUEV or if this visit is missed, plans may need to change. It may be necessary for the participant to present to the clinic for specific safety testing, return study product, etc.

5.12.1 Participant Locator Information

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.

5.12.2 HIV Counseling and Testing

HIV testing will be performed at the PUEV (Visit 23). HIV pre- and post-test counseling provided at this 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.

For participants who test HIV positive at the PUEV (Visit 23) or have ambiguous HIV testing results (i.e., positive or discordant rapid tests and negative or indeterminate Geenius), study termination should be postponed until the algorithm is completed and all necessary samples are collected.

5.12.3 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed.

5.12.4 Final Study Contact

Although the study exit visit is the last scheduled study visit, a final contact may be needed after the SEV 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 certain types of AEs that are ongoing at study exit (see SSP Section 8)

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 CRFs are completed for these contacts.

5.12.5 Referral to Non-Study Service Providers

After completing their study exit visit and final study contact, 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 —before and during their study exit visit — 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 visit (after obtaining IRB/EC approval of the written information).

5.12.6 Post-Study Contact

It is expected that all participants will be re-contacted by study staff when study results are available for dissemination.

To facilitate post-study contact with participants, locator information should be updated at the SEV, 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. A sample study exit worksheet is available on the REACH website.

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 reference above.