Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and enrolling participants in MTN-003.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

MTN-003 will enroll approximately 5000 women across participating study sites; approximately 1000 women will be enrolled in each of the five study arms. The current study accrual plan, which lists monthly accrual targets for each site, is posted on the MTN-003 web page. Accrual of all 5000 participants is targeted to be completed within a period of 24 months.

For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the MTN Coordinating and Operations Center (CORE) at FHI. Once accrual is initiated, study staff will report the number of participants screened for and enrolled in the study to the CORE (FHI) on a weekly basis. Based on this information, the CORE (FHI) will distribute a weekly consolidated cross-site accrual report to the Protocol Team. In addition, the MTN Statistical and Data Management Center (SDMC) will post reports on their ATLAS portal listing the number of participants enrolled in the study based on data received and entered into the study database. Please see Section 17 of this manual for more information on the study reporting plan.

Throughout the accrual period, the Protocol Team will review accrual and other performance data from each site to determine whether accrual targets should be adjusted across sites to achieve the study objectives most efficiently and to determine when to discontinue accrual at each site. Findings and recommendations from these reviews will be communicated to all study sites, and all sites will adjust their accrual efforts accordingly. Similar adjustments may be made after MTN Study Monitoring Committee reviews of MTN-003. The Protocol Team will make every effort to discontinue accrual approximately 14 months prior to when the targeted number of incident HIV infections (n=217) will be observed.

Throughout the accrual period, and additionally as accrual comes to an end at each site, care must be taken to manage the recruitment, screening, and enrollment process in order not to exceed site-specific accrual targets. This is important in the last 4-8 weeks of accrual at each site; during this time enrollment must be monitored closely, and potential participants must be informed that although they may undergo screening for the study, they may not be enrolled if the target sample size is reached before they are able to complete the screening and enrollment process. This may be difficult to explain to potential participants, especially those who are very interested in taking part in the study. Therefore all sites are advised to work with their community advisory board members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

Study staff are responsible for establishing study-specific participant accrual plans and updating these plans and recruitment efforts undertaken if needed to meet site-specific accrual goals.

Accrual plans should minimally contain the following elements:

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

4.2 Screening and Enrollment

Study screening and enrollment procedures are specified in the MTN-003 protocol and reflected in the visit checklists contained in Section 7 of this manual. Informed consent procedures are described in Section 5 of this manual. Guidance on performing clinical and laboratory screening procedures is included in Sections 10 and 13, respectively. Key screening and enrollment topics are described in Sections 4.2.1-4.2.10 below.

4.2.1 Definition of Screening

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in MTN-003. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.2, 7.3, and 7.4. Figure 4-1 below provides further operational guidance on the timing of assessment for each eligibility criterion. Figure 4-2 provides a mapping of interviewer-administered screening questions to the eligibility criteria these questions are intended to assess.

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish a standard operating procedure that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment/randomization
  - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of 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-003 study management team, using the following email address: mtn003mgmt@mtnstopshiv.org

Figure 4-1
Timing of Eligibility Assessments for MTN-003

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	**Assessed at Screening Part 1**	**Assessed at Screening Part 2**	**Assessed on day of Enrollment**
Inclusion Criteria			
5.2 (1) Age 18 through the site-specific upper age cap (inclusive)	X		
5.2 (2) Able and willing to provide written informed consent to be screened for and to take part in the study	X		X
5.2 (3) Able and willing to provide adequate locator information	X	X	X
5.2 (4) HIV-uninfected based on testing performed by study staff	X		X
5.2 (5) Sexually active, defined as having vaginal intercourse at least once in the 3 months prior to Screening Part 1	X		
5.2 (6) Using an effective method of contraception at enrollment and intending to use an effective method for the next 24 months (a)	X	X	X
5.2 (7) Agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the next 24 months	X	X	X
Exclusion Criteria			
5.3 (1a) Known adverse reaction to any of the study products (ever)	X		
5.3 (1b) Known adverse reaction to latex (ever)	X		
5.3 (1c) Pathologic bone fracture not related to trauma (ever)		X	X
5.3 (1d) Non-therapeutic injection drug use in the 12 months prior to Screening Part 1	X		
5.3 (1e) Post-exposure prophylaxis for HIV exposure within 6 months prior to enrollment (a)		X	X
5.3 (1f) Last pregnancy outcome 42 days or less prior to enrollment (a)	X	X	X
5.3 (1g) Gynecologic or genital procedure 42 days or less prior to enrollment (a)		X	X
5.3 (1h) Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment (a)	X	X	X
5.3 (1i) Currently breastfeeding	X	X	X
5.3 (1j) Currently using spermicide or any prohibited medication		X	X
5.3 (1k) Any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis (b)	X	X	X
5.3 (2a) AST or ALT greater than 1.5 x site ULN (c)	X		
5.3 (2b) Calculated creatinine clearance less than 60 mL/min (c)	X		
5.3 (2c) Serum creatinine greater than the site ULN (d)	X		
5.3 (2d) Hemoglobin less than 10.0 g/dl (c)	X		
5.3 (2e) Platelet count less than 100,000/mm^3 (c)	X		
5.3 (2f) Serum phosphate level below site LLN	X		
5.3 (2g) Positive for Hepatitis B surface antigen (c)	X		
5.3 (2h) Grade 2 or higher Pap result (at sites with capacity, where standard of care) (f)		X	
5.3 (2i) Dipstick urinalysis result of 2+ or greater for protein at a single visit (e)	X	[X]	[X]
5.3 (2i) At least two dipstick urinalysis results of 1+ or greater for protein at separate visits (e)	X	[X]	[X]
5.3 (2j) Any dipstick urinalysis result of 2+ or greater for glucose at a single visit	X	[X]	[X]

Figure 4-1
Timing of Eligibility Assessments for MTN-003

ELIGIBILITY CRITERIA *For ease of reference, the study eligibility criteria are abbreviated in this figure. Refer to protocol Sections 5.2 and 5.3 for complete specification of the criteria.*	**Assessed at Screening Part 1**	**Assessed at Screening Part 2**	**Assessed on day of Enrollment**
5.3 (2j) At least two dipstick urinalysis results of 1+ or greater for glucose at separate visits	X	[X]	[X]
5.3 (3) Is pregnant	X	X	X
5.3 (4a) Intends to become pregnant in the next 24 months	X		
5.3 (4b) Plans to relocate away from the study site in the next 24 months	X		
5.3 (4c) Plans to travel away from the study site for more than 8 consecutive weeks in the next 24 months	X		
5.3 (5) Diagnosed with UTI (g)	X	[X]	[X]
5.3 (6) Diagnosed with pelvic inflammatory disease or an STI or RTI requiring treatment per current WHO guidelines (h)	X	X	[X]
5.3 (7) Has a clinically apparent Grade 2 or higher pelvic exam finding (i)		X	[X]
5.3 (8) Has any other condition that, in the opinion of the IoR/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives	[X]	X	X

Notes: This figure presents minimum requirements for each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. Assessments required at Screening Part 1 and Screening Part 2 may be conducted over multiple visits/days. All assessments must be conducted within 56 days of providing informed consent for screening.

[X] = if clinically indicated

(a) Although participants are asked about these criteria at Screening Part 1 and/or Screening Part 2, the timeframe specified in the criteria is relative to the day of enrollment.
(b) Only tuberculosis is assessed at Screening Part 1.
(c) Otherwise eligible participants with exclusionary test results — other than HIV infection and Hepatitis B infection — may be re-tested during the screening process. If a participant is re-tested and non-exclusionary results are documented, the participant may be enrolled.
(d) If a participant has a serum creatinine level below the site LLN at Screening Part 1, she is eligible (with regard to the creatinine eligibility requirement) and can continue with screening procedures. However, sites should retest her creatinine level at the enrollment visit, prior to randomization. The result of the retest should not be used to determine participant eligibility, as it is not expected to be available prior to randomization. Rather, creatinine is retested at enrollment to ensure an accurate baseline value for comparison with follow-up values.
(e) If a participant is ineligible for study participation due to urine dipstick results, and the results are not related to UTI or menses, this participant should not rescreen for the study at a later time. If the abnormal dipstick results are determined to be related to UTI or menses, according to the judgment of the IoR/designee, the participant can rescreen for the study once the UTI is resolved or the participant is no longer experiencing her menses.
(f) Not required if documentation of a normal Pap result within the 12 months prior to enrollment is available.
(g) Dipstick urinalysis for leukocytes and nitrites is required at Screening Part 1 and may be performed at Screening Part 2 and/or on the day of Enrollment if clinically indicated. Otherwise eligible participants diagnosed with urinary tract infection may be enrolled after completing treatment and all symptoms have resolved.
(h) Testing is performed at Screening Part 1 for chlamydia, gonorrhea, and syphilis; testing is performed at Screening Part 2 for trichomoniasis, bacterial vaginosis (BV) (if symptomatic), and candidiasis (if symptomatic). Otherwise eligible participants diagnosed with infections requiring treatment per WHO guidelines (other than asymptomatic BV and asymptomatic

candidiasis) may be enrolled after completing treatment and all symptoms have resolved. No test of cure is required prior to enrollment.

(i) Otherwise eligible participants with exclusionary pelvic exam findings at Screening Part 2 must undergo a repeat screening pelvic exam to document improvement to a non-exclusionary severity grade or resolution prior to enrollment. Cervical bleeding associated with speculum insertion and/or specimen collection judged to be within the range of normal according to the clinical judgment of the IoR/designee is considered expected non-menstrual bleeding, and is not exclusionary.

Figure 4-2
Mapping of MTN-003 Screening Behavioral Interview Questions and Corresponding Eligibility Criteria

DEMOGRAPHICS FORM			
Form Item		**Eligibility Criterion**	
1	What is your date of birth (or age if date of birth is unknown)	5.2 (1)	Age 18 through site-specific upper age cap (inclusive)
SCREENING PART 1 ELIGIBILITY FORM			
Form Item		**Eligibility Criterion**	
1	Have you ever had a bad reaction to latex (such as latex condoms or gloves)?	5.3 (1b)	Known adverse reaction to latex (ever)
2 3	Have you ever used tenofovir gel, tenofovir tablets, or Truvada tablets? (If yes) Have you ever had a bad reaction to tenofovir gel, tenofovir tablets, or Truvada tablets?	5.3 (1a)	Known adverse reaction to any of the study products (ever)
4	In the past 1 year (12 months), have you used a needle to inject drugs that were not prescribed to you by a medical professional?	5.3 (1d)	Non-therapeutic injection drug use in the 12 months prior to Screening Part 1
5	In the past 3 months, have you had vaginal sex?	5.2 (5)	Sexually active, defined as having vaginal intercourse at least once in the 3 months prior to Screening Part 1
9	In the past 6 weeks (42 days), have you been pregnant, given birth (including stillbirth), or had a pregnancy terminated?	5.3 (1f)	Last pregnancy outcome 42 days or less prior to enrollment
10	Are you breastfeeding now?	5.3 (1i)	Currently breastfeeding
11 12	Do you and your partner plan to have a child in the future? (If yes) When do you and your partner intend to have your future child?	5.3 (4a)	Intends to become pregnant in the next 24 months
13	If you were to join this research study, would you be willing to use a reliable method of contraception for the next 2 years (24 months)? The methods that are considered reliable include: oral contraceptive pills, contraceptive injections (for example, depo provera), contraceptive implants (for example, norplant or jadelle), contraceptive patches, intrauterine contraceptive devices, and surgical sterilization of you or your partner(s).	5.2 (6)	Using an effective method of contraception at enrollment and intending to use an effective method for the next 24 months

Figure 4-2
Mapping of MTN-003 Screening Behavioral Interview Questions and Corresponding Eligibility Criteria

14	Do you plan to move away from this area in the next 2 years (24 months)?	5.3 (4b)	Plans to relocate away from the study site in the next 24 months
15	Do you plan to be away from this area for more than 8 weeks in a row in the next two years (24 months)? This includes seasonal travel, travel for farming, trade, or other purposes.	5.3 (4c)	Plans to travel away from the study site for more than 8 consecutive weeks in the next 24 months
16	In the past 30 days, have you taken part in any other research study of medicines, medical devices, or vaginal products?	5.3 (1h)	Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
17	If you were to join this study, would you agree to not take part in any other research study of medicines, medical devices, or vaginal products for the next 2 years (24 months)?	5.2 (7)	Agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the next 24 months
18 19	Do you currently have tuberculosis, also known as TB? Are you currently taking any medication used to treat tuberculosis or TB?	5.3 (1k)	Any significant uncontrolled active or chronic cardiovascular, renal, liver, hematologic, neurologic, gastrointestinal, psychiatric, endocrine, respiratory, immunologic disorder or infectious disease, including active tuberculosis
SCREENING PART 2/ENROLLMENT BEHAVIORAL ELIGIBILITY FORM			
Form Item		**Eligibility Criterion**	
1	In the past 6 weeks (42 days), have you been pregnant, given birth (including stillbirth), or had a pregnancy terminated?	5.3 (1f)	Last pregnancy outcome 42 days or less prior to enrollment
2	Are you breastfeeding now?	5.3 (1i)	Currently breastfeeding
3	Which method of contraception are you currently using?	5.2 (6)	Using an effective method of contraception at enrollment and intending to use an effective method for the next 24 months
4	If you were to join this study, would you be willing to use a reliable method for the next 2 years (24 months)? The methods that are considered reliable include: oral contraceptive pills, contraceptive injections (for example, depo provera), contraceptive implants (for example, norplant or jadelle), contraceptive patches, intrauterine contraceptive devices, and surgical sterilization of you or your partner(s).	5.2 (6)	Using an effective method of contraception at enrollment and intending to use an effective method for the next 24 months
5	In the past 30 days, have you taken part in any other research study of medicines, medical devices, or vaginal products?	5.3 (1h)	Participation in any other research study involving drugs, medical devices, or vaginal products 30 days or less prior to enrollment
6	If you were to join this study, would you agree to not take part in any other research study of medicines, medical devices, or vaginal products for the next 2 years (24 months)?	5.2 (7)	Agrees not to participate in other research studies involving drugs, medical devices, or vaginal products for the next 24 months

4.2.1.1 Assessment of Acute HIV Infection Prior to Enrollment

To ensure that participants who are enrolled in the study are not in the acute stage of HIV infection, when antibody tests are typically negative, any participant who presents at the enrollment visit with symptoms suggestive of acute viral infection should not be enrolled on that day. Enrollment should instead be postponed until these symptoms have resolved and subsequent HIV status is confirmed as negative. Acute HIV infection is defined as the period of rapid viral replication that immediately follows the initial establishment of infection with HIV. Symptoms of acute HIV infection may be indistinguishable from a typical viral syndrome, and can include:

- fever
- fatigue
- headache
- myalgia
- weight loss
- pharyngitis or sore throat
- lymphadenopathy
- rash
- diarrhea

Because these symptoms are common in other viral illnesses such as influenza ("the flu") or mononucleosis, it is important to assess the constellation and duration of symptoms (most common symptoms include fever, fatigue, headache, myalgia, and sore throat) and possible causes. The PSRT may also be consulted to assist with decisions about postponing enrollment in participants in whom acute HIV infection is considered.

Participants for whom enrollment was postponed due to concern for acute HIV infection should have repeat HIV testing no earlier than 4 weeks following the prior negative HIV test. If the HIV antibody test is negative at that point, and the participant no longer has symptoms suggestive of acute viral infection, the participant may be enrolled in the study, assuming no other interim contraindications are noted. If an alternative diagnosis for the symptoms is identified (for example, malaria or influenza) then the enrollment visit may be re-scheduled sooner, once all symptoms have been resolved.

4.2.2 Screening Visit Locations

Because of the nature of study procedures required to be performed at MTN-003 screening visits, all visits are expected to be completed at the study clinic.

4.2.3 Definition of Enrollment

Participants will be considered enrolled in MTN-003 when they have been assigned a MTN-003 Clinic Randomization Envelope. Further information on methods and materials for random assignment is provided in Section 4.2.10.

4.2.4 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place up to 56-days prior to enrollment, beginning on the day the potential participant provides written informed consent for screening. In other words, the day the screening informed consent is signed is counted as "-56" and enrollment is counted as Day 0. For example, as shown below, a potential participant who provides written informed consent for screening on 7 September 2010 could be enrolled on any day up to and including 2 November 2010.

September 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
			1	2	3	4
5	6	**7 Screening Consent** (day -56)	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30		

October 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30
31						

November 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1	**2 Last Day to Enroll** (day 0)	3	4	5	6

If all screening and enrollment procedures are not completed up to 56 days of obtaining written informed consent for screening, the participant must repeat the entire screening process, beginning with the screening informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case (see Section 4.2.7 below). The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time she provides written informed consent for screening).

4.2.5 Enrollment Split Visits

Per Protocol, Section 7.4.1, the Enrollment Informed Consent (IC) will be administered once the participant meets all eligibility criteria; however, the IC process may precede final confirmation of eligibility if doing so decreases participant burden (e.g. multiple venipunctures). A site-specific SOP should specify when the IC is to be administered at each site; this process should be consistent for all participants at the site. If for some reason the participant cannot complete the enrollment visit on that day (e.g. participant has to leave early due to an emergency), when she returns to the clinic to complete her enrollment visit, all confirmation of eligibility procedures listed in Section 7.4.1 of the protocol must be repeated; however, the Enrollment IC process does not need to be repeated. All enrollment procedures must occur within the 56-day screening window based on the date of screening informed consent.

4.2.6 Screening and Enrollment Logs

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. A sample screening and enrollment log suitable for use in MTN-003 is shown in Figure 4-3. Study sites are encouraged to reference the eligibility criteria item numbers in protocol Sections 5.2 and 5.3 when recording the reason for screening failure/discontinuation on the screening and enrollment logs; these item numbers are also shown in Figure 4-1.

Figure 4-3
Sample Screening and Enrollment Log for MTN-003

	Screening Attempt	Screening Date(s)	Participant ID	Enrollment Date (or NA if not enrolled)	Screening Failure/ Discontinuation Date (or NA if enrolled)	Reason for Screening Failure/Discontinuation (or NA if enrolled)
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						

4.2.7 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-003. As shown in Figure 4-4, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Further information regarding the structure of PTIDs for MTN-003 can be found in Section 14 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-4
Sample Site-Specific PTID List for MTN-003

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

4.2.8 Screening HIV Testing

Screening HIV testing will be performed using two different rapid HIV tests per the algorithm in protocol Appendix II. At least one of the two rapid tests must be FDA-approved and each site's test kit selections must be validated and approved by the MTN Network Laboratory (NL). Always contact the NL in cases of unusual test results or problems with testing methods.

Screening HIV testing will be performed at Screening Part 1 and on the day of enrollment as part of final eligibility determination prior to random assignment:

- If both rapid tests are negative, the participant will be considered HIV-uninfected; no further testing is required.
- If both rapid tests are positive, the participant will be considered HIV-infected, and therefore ineligible for the study; no further testing is required.
- If the two rapid tests are discordant, an FDA-approved Genetic Systems Western blot (WB) test, manufactured by Bio-Rad Laboratories, will be performed.

- If the WB is negative, the participant will be considered HIV-uninfected; no further testing is required.

- If the WB is positive, the participant will be considered HIV-infected, and therefore ineligible for the study; no further testing is required.

- If the WB is indeterminate, the participant will be asked to present to the study site in approximately one month for re-testing. At that time, the two rapid tests will be repeated and the above-described algorithm will be followed.

All sites should notify the NL in the event that discordant rapid HIV test results are obtained. This notification is for informational purposes; while the NL may provide technical guidance to the site if needed, WB testing at the local lab should proceed immediately upon identification of the discordant rapid test results.

Guidelines for performing HIV tests during screening are provided in Section 13 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents; such documents must capture the start and end/read times for each test. 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 specified timeframes for the tests and prior to disclosure of results to participants. 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.

4.2.9 Eligibility Screening Scenarios

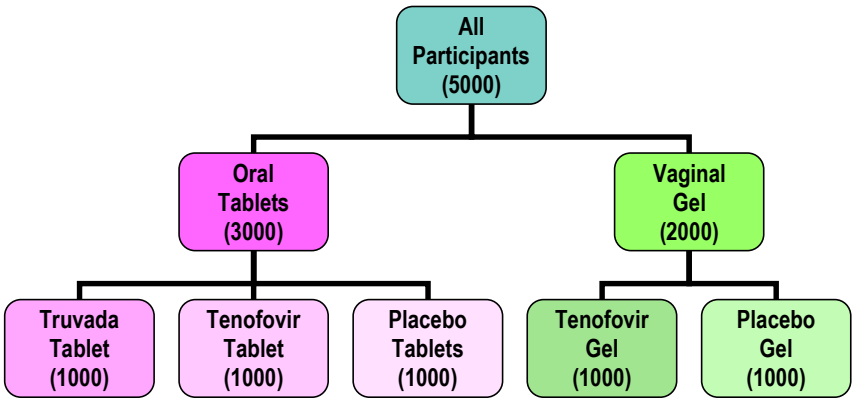
Several sample eligibility screening scenarios are provided to each study site during study-specific training. Study staff are encouraged to use these scenarios for reference and refresher training throughout the study accrual period. Additional scenarios also will be posted for review and cross-site discussion on the MTN-003 Clinical Discussion Board (accessible through the MTN SDMC's ATLAS portal) throughout the accrual period.

4.2.10 Random Assignment

4.2.10.1 Overview

At all sites, participants will be randomly assigned in equal numbers to the five study arms. Across sites, as shown in Figure 4-5, approximately 1000 women will be assigned to each arm.

Figure 4-5
MTN-003 Participant Randomization Scheme



In Figure 4-5, the five study arms are identified using the terminology used in study educational and counseling materials. Corresponding to each of the five arms shown, participants will be assigned to one of the following study product regimens:

- Truvada tablet: one emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) tablet and one tenofovir disoproxil fumarate (TDF) placebo tablet taken by mouth every day
- Tenofovir tablet: one TDF tablet and one FTC/TDF placebo tablet taken by mouth every day
- Placebo tablets: one TDF placebo tablet and one FTC/TDF placebo tablet taken by mouth every day
- Tenofovir gel: contents of one applicator of tenofovir 1% gel inserted vaginally every day
- Placebo gel: contents of one applicator of placebo gel inserted vaginally every day

Note: To preserve blinding, each oral tablet regimen involves taking two tablets every day.

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

- MTN-003 Clinic Randomization Envelopes
- MTN-003 Clinic Randomization Envelope Tracking Records (Figure 4-6)
- MTN-003 Prescriptions (Figures 4-7 and 4-8)
- MTN-003 Pharmacy Randomization Envelopes
- MTN-003 Pharmacy Randomization Envelope Tracking Records
- MTN-003 Participant-Specific Pharmacy Dispensing Records

Clinic Randomization Envelopes will be shipped from the MTN SDMC to each study clinic. They will be stored in the clinic and assigned in sequential order (via increasing envelope number) to participants who have been confirmed as eligible and have provided written informed consent to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with security tape that, when opened, reveals the word "OPENED" or "SECURITY TAPE" in the residue of the tape.

Envelope assignment to eligible participants will be documented on the Clinic Randomization Envelope Tracking Record that will accompany each envelope shipment to each site (Figure 4-6). The act of assigning a Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once a Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each Clinic Randomization Envelope will contain a prescription (Figures 4-7 and 4-8). Prescriptions will be produced as two-part no carbon required (NCR) forms pre-printed with the site (CRS) name, DAIDS site ID number, site (CRS) location, randomization envelope number, and a random assignment to either "Vaginal Gel" or "Oral Tablets." After recording the PTID and other details on the prescription, clinic staff will separate the two sheets of the form and the white original will be delivered to the pharmacy. The envelope and the yellow copy will be retained in the participant's study notebook in the clinic.

Figure 4-6
Sample MTN-003 Clinic Randomization Envelope Tracking Record

MTN 003 Clinic Randomization Envelope Tracking Record

Page ☐☐

CRS Name:	Pre-print	DAIDS Site ID:	Pre-print
CRS Location:	Pre-print		

Instructions: Complete one row each time a clinic randomization envelope is assigned to an MTN 003 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

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

Figure 4-7
Sample MTN-003 Prescription — Oral Tablets

MTN-003 PRESCRIPTION

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

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

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-003? ..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

Assignment: Oral Tablets

Tenofovir Disoproxil Fumarate 300 mg Or Placebo

Sig: Take one (1) tablet by mouth once each day as directed.

Quantity: Sufficient to last until next study visit (as requested by designated clinic staff). May be refilled as needed (as requested by designated clinic staff) for duration of participation in the study.

Emtricitabine 200 mg/Tenofovir Disoproxil Fumarate 300 mg Or Placebo

Sig: Take one (1) tablet by mouth once each day as directed.

Quantity: Sufficient to last until next study visit (as requested by designated clinic staff). May be refilled as needed (as requested by designated clinic staff) for duration of participation in the study.

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction: Complete all items in this box. After signing and dating, deliver white copy to pharmacy. File yellow copy in participant study notebook.

Pharmacy: Dispense ☐ bottles of TDF 300mg or placebo (30 tablets/bottle) **AND**

☐ bottles of FTC/TDF 200mg/300mg or placebo (30 tablets/bottle) to participant as directed in protocol.

Clinic Staff Initials: _____ Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Figure 4-8
Sample MTN-003 Prescription — Vaginal Gel

MTN-003 PRESCRIPTION

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

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

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into MTN-003? ..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

Assignment: Vaginal Gel

MTN-003 Study Gel (Tenofovir 1% Gel or Placebo)

Sig: Insert entire contents of 1 applicator vaginally once each day as directed.

Quantity: Sufficient to last until next study visit (as requested by designated clinic staff). May be refilled as needed (as requested by designated clinic staff) for duration of participation in the study.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction: Complete all items in this box. After signing and dating, deliver white copy to pharmacy. File yellow copy in participant study notebook.

Pharmacy: Dispense ☐ cartons of study gel (10 applicators/carton) to participant as directed in protocol.

Clinic Staff Initials: _____ Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy Randomization Envelopes will be shipped from the MTN SDMC to the Pharmacist of Record (PoR) at each site pharmacy. These envelopes are prepared in a similar fashion to the Clinic Randomization Envelopes and are linked to the Clinic Randomization Envelopes by envelope number. They will be stored in the study pharmacy and opened by pharmacy staff upon receipt of a prescription bearing the corresponding Clinic Randomization Envelope number. Assignment of each envelope to an enrolled study participant will be documented on the Pharmacy Randomization Envelope Tracking Record that will accompany each envelope shipment to the site pharmacy. Further information on the contents and management of Pharmacy Randomization Envelopes is provided in the *MTN-003 Pharmacist Study Product Management Procedures Manual*.

4.2.10.2 Participant-Specific Procedures

For each participant, random assignment will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking an informed consent form for enrollment. Random assignment also will take place after the participant has:

- Completed the informed consent process for specimen storage and possible future research testing *(unless this informed consent process is deferred to the Month 1, 2, or 3 visit)*.
- Completed the Baseline Behavior Assessment form
- Completed the Baseline ACASI Questionnaire
- Provided blood for plasma archive
- Received Hepatitis B vaccine, if clinically indicated and accepted by the participant

The in-clinic randomization procedures listed below (Steps C1-C6) then will be performed.

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

C2. Open the assigned Clinic Randomization Envelope; alternatively, allow the participant to open it. Remove the prescription from the envelope and verify that the envelope number printed on the prescription corresponds to the envelope number printed on the Clinic Randomization Envelope label. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the MTN-003 study management team and site Pharmacist of Record (PoR) immediately. The PoR will inform the DAIDS Protocol Pharmacist. Do not proceed with randomization of this or any other participant until instructed to do so by the MTN SDMC.

C3. Inform the participant of her assignment — to either vaginal gel or oral tablets— and provide appropriate information, instructions, and counseling applicable to her assignment. Refer to study-specific informed consent support materials and other study informational materials as needed.

C4. Complete the prescription as follows:

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

The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study product. This person must be listed as an investigator (either IoR or sub-investigator) on the current FDA Form 1572. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.

The bottom section of the prescription may be completed by a study staff member authorized in the site's delegation of duties to determine the quantity of product to be dispensed to study participants. This person may be the authorized prescriber who completes the middle section of the prescription or may be another clinic staff member. If this section is completed by a staff member other than the person who opened the Clinic Randomization Envelope, the clinic staff member who completes this section must have access to source documentation of the date upon which the Clinic Randomization Envelope was opened.

C5. Double-check the accuracy of all entries and then separate the two sheets of the completed prescription. Retain the yellow copy in the participant study notebook in the clinic. Also retain the Clinic Randomization Envelope in the participant study notebook. Clinic Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.

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

Corresponding to steps C1-C6 above, in-pharmacy randomization procedures are specified in the *MTN-003 Pharmacist Study Product Management Procedures Manual*. If pharmacy staff identify possible errors on the original prescription, they will return the prescription to clinic staff for clarification or correction. If corrections are required, corrections must be made on both the white original prescription and the yellow copy by the authorized prescriber. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete original prescriptions.

4.3 Product Use Instructions, First Product Use, and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions for daily use of their assigned product, followed by adherence counseling. Participants also will complete their first product use at the clinic during their enrollment visits. Further guidance related to product use instructions, first product use, and adherence counseling is provided in Section 12 of this manual.