Section 4. Participant Accrual

This section provides information on requirements and procedures for recruiting, screening, and randomizing/enrolling participants onto HPTN 059.

4.1 Study Accrual Plan and Site-Specific Accrual Targets

The accrual targets will be 100 women for the India site and 100 women across US sites.

- Table 4-1 presents monthly accrual targets for each site. For each site, accrual will begin after all applicable approvals are obtained and a site-specific study activation notice is issued by the HPTN Coordinating and Operations Center (CORE). Approximately 100 women will be recruited at the Pune, India site, and 100 women will be recruited across US sites. (See Protocol Section 7.3 for additional detail on Participant Accrual)

Table 4-1
HPTN 059 Accrual Plan – Participants Enrolled Per Month

ACCRUAL MONTH	ACCRUAL TARGETS	
	Pune, India	**BLHC + UAB=US Sites**
1	8	7+7=14
2	14	7+7=14
3	18	10+10=20
4	20	10+10=20
5	20	10+10=20
6	20	6+6=12
TOTAL	**100 women**	**50+50=100 women**

Once accrual is initiated at each site, study staff will report the number of participants screened for and enrolled in the study to the HPTN CORE on a weekly basis. To facilitate weekly reporting, the international site will use the HPTN 059 Participant Tracking Database provided by CORE, and it will include a pre-programmed report of required accrual information. The US sites will use site developed tools for participant tracking. Based on information received from each site, the CORE will distribute a consolidated cross-site accrual report to the Protocol Team. The SDMC will report to the Protocol Team the number of participants enrolled based on data received and entered into the study database (Refer to Section 15.2.1).

Note: *The Participant Tracking Database is used for tracking purposes only. It must not to be used to record source data or to generate source documents. All information entered into the database must be based on other source documents contained in participants' study charts.*

Approximately every three months during the accrual period, the Protocol Team will review performance and data from each site to determine whether accrual targets must 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 each study site, and the sites will adjust their accrual efforts accordingly. The Protocol Team will make every effort to complete accrual approximately 6 months from study initiation.

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, since during this time enrollment must be monitored closely, and potential participants must be informed that although they may screen 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 both sites are advised to work with their community advisory board/group members to develop strategies to address this issue several weeks to months before the end of accrual at the site.

Site staff is responsible for establishing a standard operating procedure (SOP) for participant accrual and for updating the SOP and recruitment efforts undertaken if needed to meet site specific accrual goals. The accrual SOP minimally must contain the following elements:

- Site-specific accrual goals
- Methods for tracking actual accrual versus accrual goals
- Recruitment methods and venues
- Methods for identifying the recruitment source of participant who present to the site for screening
- Methods for timely evaluation of the utility 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)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Screening and Enrollment

The study screening and enrollment procedures are described in detail in the protocol and visit checklists contained in Sections 2 and 7 of this manual, respectively. Informed consent procedures are described in Section 5 and instructions for performing clinical and laboratory screening procedures are included in SSP Sections 10 and 12, respectively. Several possible screening and enrollment scenarios are presented for illustrative purposes in Section Appendix 4-1.

4.2.1 Definition of Screening

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in HPTN 059. The study eligibility criteria are listed in protocol Sections 3.1 and 3.2. Figure 4-2 provides further information on the timing of assessment for each eligibility criterion. Required screening procedures are listed in protocol Sections 5.1 and 5.2, and protocol Appendix I.

It is the responsibility of the site Investigator of Record 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 an SOP that describes how study staff will fulfill this responsibility. This SOP minimally must contain the following elements:

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

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee must contact the HPTN 059 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 11 of this manual. Site staff must also complete a protocol event form in accordance with the guidelines of Section 12.4 of the Manual of Operating Procedures, http://www.hptn.org/MOP2005/HPTNMOP2005.htm

Table 4-2
Timing of Eligibility Assessments for HPTN 059

Inclusion and Exclusion Criteria	Assessed At Screening	Assessed At Final Screening/Enrollment
Between the ages of 18 and 50 at the time of enrollment as verified by site SOP	X	
Be willing and able to provide written informed consent	X	X
Be in general good health	X	X
Be HIV uninfected	X	X
Have a normal Pap Test, or be able to Document a normal Pap Test (90 days prior to screening)	X	
Be sexually active, defined as having had penile-vaginal intercourse at least once in 30 days	X	
Be willing to use an effective method of contraception during the study, defined as either a hormonal based method (except vaginal rings); an IUD; female sterilization, or sexual activity with a vasectomized partner	X	
Be willing to undergo all study related assessments (clinical and laboratory), including speculum examination, colposcopy, urine testing and blood draws, and, adhere to follow up schedule as required by the protocol	X	X
Agree not to participate in spermicide and/or vaginal microbicides study or any other device or drug study	X	
Has participated in any other spermicide and/or vaginal microbicide study or any device or drug in the 30 days prior to enrollment	X	X
Menopausal or post menopausal	X	X
Hysterectomy	X	
History of adverse reaction to latex	X	
Taking systemic tenofovir, adefovir or any chronic hepatitis B medications, or plan to while participating in this study	X	X
History of adverse reaction to tenofovir and/or adefovir	X	
Pregnant, based on self report or testing performed by study staff	X	X
Within 90 days of last pregnancy outcome[a]	X	X
Grade 3 or higher laboratory abnormality, as defined by the DAIDS Table for Grading Adult and Pediatric Adverse Experiences, based on hematology, liver and renal function, and coagulation testing performed by study staff	X	

Table 4-2 continued
Timing of Eligibility Assessments for HPTN 059

Had a gynecological procedure 90 days prior to enrollment	X	X
Have an STI or RTI according to CDC guidelines, via laboratory tests or on examination, and requiring treatment	X	X
History of injecting non-therapeutic drugs intravenously in the 12 months prior to enrollment	X	X
History of vaginal intercourse more than an average of 2 times per day in the two weeks prior to screening	X	
Breastfeeding	X	X
Has any other condition that, in the opinion of the site investigator, would preclude provision of informed consent, make participation in the study unsafe, complicate interpretation of outcome data, or otherwise interfere with achieving the study objectives		X

This schedule presents minimum requirements for ascertainment of each eligibility criterion. Additional assessments related to any criterion may be performed if clinically indicated. Assessments required at Screening may be conducted over multiple visits/days. All Enrollment assessments must be conducted within 56 days of providing informed consent for screening, and with the exception of Informed Consent for Enrollment and Specimen Storage, must be completed at a single study visit. Informed Consent for Enrollment and Specimen Storage may be discussed and obtained prior to the Enrollment Visit as needed.

[a] Although participants will be asked about pregnancy history, history of gynecological procedures, and history of non-therapeutic injection drug use at Screening, the 90-day time frame for these criteria only is relative to the day of enrollment. Similarly, although participants will be asked about participation in any other spermicide and/or vaginal microbicide study or any device or drug study at Screening, the 30-day time frame for this criterion is relative to the day of Enrollment.

4.2.2 Definition of Enrollment

Participants will be considered enrolled in HPTN 059 once the assigned HPTN 059 Clinic Randomization Envelope has randomization envelope had been opened. Further information on methods and materials for random assignment is provided in Section 4.2.7.

4.2.3 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place within a 56-day period, beginning on the day the potential participant provides written informed consent for screening. For example:

- A potential participant who signs or marks her screening informed consent form on July 1 could be enrolled on any day up to and including August 26.

July 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
					1 **Screening Consent**	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						

August 2005						
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 **Last Day to Enroll**	27
28	29	30	31			

For the International site, the HPTN 059 Participant Tracking Database is pre-programmed to calculate the allowable 56-day screening window for each potential participant, beginning on the day when she signs or marks her screening informed consent form. To help ensure that the 56-day screening period is not exceeded, study staff are strongly encouraged to highlight the allowable screening period on their screening and enrollment visit checklists (as shown in Section 7 of this manual).

For the US sites, each site will develop a participant tracking tool, to ensure that the 56-day screening period is not exceeded, and to ensure that participants visit windows are adhered to.

If all screening and enrollment procedures are not completed within 56 days of obtaining informed consent for screening, the participant must repeat the entire screening process, including the screening informed consent process, but not including PTID assignment, which is not repeated. The term "screening attempt" is used to describe each time a participant screens for the study.

4.2.4 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Figure 4-3 presents a sample screening and enrollment log suitable for use in HPTN 059. Study sites are encouraged to reference the item numbers on the Screening Summary non-DataFax form (see Section 13.6) when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

Figure 4-3
Sample Screening and Enrollment Log for HPTN 059

	Screening Attempt	Screening Date(s)	Date Screening Consent Signed	Participant ID	Date Enrollment Consent Signed	Enrollment Date(or NA if not enrolled)	Cohort	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									

4.2.5 Assignment of Participant ID Numbers

SDMC will provide each study site with a listing of Participant ID (PTID) numbers for use in HPTN 059. As shown in Figure 4-4, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site.

Further information regarding the structure of PTIDs for HPTN 059 can be found in Section 13. PTIDs will be assigned to all potential participants who come to the clinic for a screening visit, regardless of whether they provide written inform consent or they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts she undergoes. Site staff are responsible for establishing SOPs, proper storage, handling, and maintenance of the PTID list. Participant confidentiality must be maintained so individual PTIDs are assigned to only one participant, and individual participants are assigned to only one PTID.

Figure 4-4
Sample Site-Specific PTID List for HPTN 059

	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			

4.2.6 Screening HIV Testing

HIV infection status at screening will be assessed using an FDA-approved enzyme immunoassay (EIA), illustrated in Appendix III of the protocol. If the EIA is non-reactive, the participant will be considered HIV-uninfected. If the EIA is reactive, the FDA-approved Genetic Systems WB test, manufactured by Bio-Rad Laboratories, will be performed. If the WB is negative, the participant will be considered HIV-uninfected. If the WB is positive, the participant will be considered HIV-infected, and therefore ineligible for the study. If the WB is indeterminate, the participant will be asked to return to the study site in approximately one month for re-testing.

Further instructions for performing HIV tests during screening are provided in Section 12.5.2. At each site, all tests must be documented on local laboratory log sheets or other laboratory source documents. Also at each site, 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 prior to disclosure of results to participants (Refer to SSP Section 12 on Laboratory Considerations).

4.2.7 Random Assignment

Overview

At each study site, enrolled participants will be randomly assigned in equal numbers to the four study treatment arms. The study arms will be double-blinded to Study Gel, meaning that the clinic staff and participants, with exception of the DAIDS protocol pharmacist, will not be provided information on the identity of the specific gels to which participants in the gel groups have been assigned. Site pharmacists will be the only site staff members unblinded to product assignment.

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

- HPTN 059 Clinic Randomization Envelopes
- HPTN 059 Clinic Randomization Envelope Tracking Records
- HPTN 059 Prescriptions (coitally dependent and daily use)

- HPTN 059 Participant – specific Pharmacy Dispensing Records

HPTN 059 Clinic Randomization Envelopes will be shipped from the SDMC to each study site. They will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an HPTN 059 Clinic Randomization Envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape.

HPTN 059 Clinic Randomization Envelope assignment to eligible participants will be documented on the HPTN 059 Clinic Randomization Envelope Tracking Records (see Figure 4-5) that will accompany the initial envelope shipment to each site. The act of assigning an HPTN 059 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study. Once an HPTN 059 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each HPTN 059 Clinic Randomization Envelope will contain an HPTN 059 prescription (see Figures 4-6a and 4-6b). HPTN 059 Prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the site name, site number, clinic name, HPTN 059 Clinic Randomization Envelope number, coded information indicating assignment to either tenofovir gel or placebo gel, and frequency assignment to either coitally dependent or daily use. After recording the PTID and signature on the prescription, clinic staff will separate the two parts of the Prescription form and deliver or fax the white original copy to the pharmacy. The HPTN 059 Clinic Randomization Envelope and the yellow copy of the prescription will be retained in the participant's study notebook. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

HPTN 059 Participant-specific Pharmacy Dispensing Records will be shipped from the SDMC to each study pharmacy, and will be used by pharmacy staff to document dispensation of study gel cartons to the participant. These records will be pre-printed with the site name, site number, clinic name, HPTN 059 Clinic Randomization Envelope number, coded information indicating assignment to either tenofovir gel or placebo gel, and frequency assignment to either coitally dependent or daily use, and will contain a space to adhere the tear-off labels (containing unblinded product information) of dispensed cartons of study gel. Site pharmacy staff only will have access to the Participant-specific Pharmacy Dispensing Records. Pharmacy staff will store all study related pharmacy records, and anything related to the study, securely in the study pharmacy; unblinded product will be kept strictly confidential, with access limited to site pharmacy staff only. (Refer to protocol Section 4).

Figure 4-5
Sample HPTN 059 Clinic Randomization Envelope Tracking Record

Site Name:	Pre-print	Site Number:	Pre-print
Clinic Name:	Pre-print		

Page ☐☐

Instructions: Complete one row each time a HPTN 059 Clinic Randomization Envelope is assigned to an HPTN 059 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 4-6a
Sample HPTN 059 Prescription — Coitally Dependent Arm

HPTN 059 PRESCRIPTION

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

Site Name:	**Pre-print**	Site Number:	**Pre-print**
Clinic Name:	**Pre-print**	Clinic Randomization Envelope #:	**Pre-print**
Randomization Code:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into HPTN 059? ..... *yes* ☐ *no* ☐ Clinic Staff Initials:_____

Frequency Assignment: Coitally Dependent

HPTN 059 Study Gel

Sig: Insert one applicatorful vaginally up to 2 hours before each act of penile-vaginal sexual intercourse for a maximum of twice daily.

Quantity: Sufficient to last until next study visit. Refill as authorized by designated clinic staff for a period of 24 weeks, unless otherwise directed by designated clinic staff.

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature:_____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction for Initial Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense ☐ cartons of study gel (10 tubes/applicators per carton) to participant.

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

Pharmacy

rx_gel_coital_final_14Feb06.doc

Figure 4-6b
Sample HPTN 059 Prescription — Daily Use Arm

HPTN 059 PRESCRIPTION

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

Site Name:	**Pre-print**	Site Number:	**Pre-print**
Clinic Name:	**Pre-print**	Clinic Randomization Envelope #:	**Pre-print**
Randomization Code:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐☐–☐

Did participant provide written informed consent for enrollment into HPTN 059? ..... *yes* ☐ *no* ☐ Clinic Staff Initials:_____

Frequency Assignment: Daily Use

HPTN 059 Study Gel

Sig: Insert one applicatorful vaginally once each day at bedtime (or period of longest rest).

Quantity: Sufficient quantity to last until next study visit. Refill as authorized by designated clinic staff for a period of 24 weeks, unless otherwise directed by designated clinic staff.

Authorized Prescriber Name (please print):_____

Authorized Prescriber Signature:_____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instruction for Initial Dispensing Only: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense ☐ cartons of study gel (10 tubes/applicators per carton) to participant.

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

Pharmacy

rx_gel_daily_final_14Feb06.doc

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 the enrollment informed consent form. Random assignment also will take place after the participant has completed the Enrollment Behavior Assessment and has provided blood for the plasma and serum archive. The in-clinic randomization procedures listed below will be performed. Several possible randomization and first gel dispensation scenarios are presented for illustrative purposes in Section Appendix 4-2.

In Clinic:

C1. Obtain the next sequential HPTN 059 Clinic Randomization Envelope and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the HPTN 059 Clinic Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and authorized clinic staff initials in the row corresponding to the assigned envelope number.

C2. Open the assigned HPTN 059 Clinic Randomization Envelope; or, allow the participant to open it herself. Remove the prescription and confirm the information pre-printed at the top of the form. In particular, confirm that the envelope number printed on the prescription corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the SDMC Project Manager 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 SDMC.

C3. Inform the participant of her frequency assignment (daily use or coitally dependent) and provide appropriate information, instructions, and counseling applicable to her assignment. Refer to study-specific informed consent support materials and the Frequently Asked Gel Use Questions in Section Appendix 9-1 for reference as needed.

C4. Complete the prescription, as follows:

- In the top section of the prescription, record the PTID and mark whether the participant provided informed consent to take part in the study. The staff member 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 staff initials beside these boxes.
- The middle section of the prescription must be completed by a study staff member designated in the site's delegation of duties as an authorized prescriber of study gel. This person also must be listed as an investigator (either the Investigator of Record 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 any clinic staff member

authorized in the site's delegation of duties to determine the quantity of gel to be given to study participants. Once randomized, participants in the daily group will receive 4 cartons of study gel at the Enrollment Visit. Participants in the coitally dependent group will receive 8 cartons of study gel at the Enrollment Visit. After the Enrollment visit, clinic staff will use the Gel Re-supply Worksheet to determine the number of cartons participants in the coitally dependent group should receive at subsequent follow up visits. Participants assigned to the daily use frequency group will receive a standard quantity of 4 cartons of study gel at each scheduled study visit.

C5. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain and place the yellow copy in the participant study notebook. Also retain and place the HPTN 059 Clinic Randomization Envelope in the participant study notebook. HPTN 059 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, as follows:

- OPTION A: Give the original prescription to the participant to deliver to the pharmacy
- OPTION B: Deliver the original prescription to the pharmacy
- OPTION C: Fax a copy of the original prescription to the pharmacy for filling purposes only; deliver the original prescription to the pharmacy by the time of gel pick-up

Note: *In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, identical corrections must be made on both the white original prescription and the yellow copy. An identical signed and dated note explaining the corrections also must be recorded on both copies. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions.*

C7. Once the site pharmacist of record has given study gel to the participant, a member of clinic staff will obtain from the site pharmacist (as specified in a site SOP) the four-digit unique identifying number printed on the first carton of study drug given to the participant. This number and the number of cartons first dispensed should be recorded on the participant's Enrollment form.

Section Appendix 4-1
Screening and Enrollment Scenarios for HPTN 059

4-1.1 Suppose Miss X begins the study screening process (i.e., signs or marks the screening informed consent) on July 1, and that based on the protocol-specified screening visit procedures she appears to be eligible for the study. When Miss X's screening lab results are received, however, she is found to have chlamydia. What do you do?

- When Miss X returns for Final Screening/Enrollment (for example on July 11), provide results and chlamydia treatment and continue the screening and enrollment process. Ideally single-dose treatment will be provided, so that if Miss X is otherwise eligible for the study and free of STI/RTI symptoms, she may be enrolled at this visit.If single dose treatment is not provided, schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STI/RTI symptoms at that time).

Why? Potential participants diagnosed with an STI or RTI during the screening process must complete treatment and be free of STI/RTI symptoms in order to be eligible for the study.

4-1.2 Continuing from Scenario 4-1.1, suppose Miss X is given a seven-day course of treatment on July 11 and returns to the study site on July 18. What should you do?

- On July 18 confirm that Miss X completed the seven-day course of treatment. If Miss X reports having completed treatment, proceed with the enrollment process. If Miss X reports not having completed treatment, provide education and counseling to encourage completion of treatment and provide additional medication if needed. Schedule Miss X to return to the study site to complete the enrollment process immediately after treatment has been completed (assuming she remains free of STI/RTI symptoms at that time).

Why? Potential participants diagnosed with an STI during the screening process must complete STI treatment and be free of STI/RTI symptoms in order to be eligible for the study.

Appendix 4-1 Continued
Screening and Enrollment Scenarios for HPTN 059

4-1.3 Continuing from Scenario 4-1.2, suppose Miss X is given a seven-day course of treatment on July 11 but does not return to the study site until September 8. What do you do?

- Begin the entire screening process again from the beginning (including the screening informed consent process, but not including assignment of a new PTID).

Why? All screening and enrollment procedures must be completed within 56 days. If more than 56 days elapse from the day when the participant signed or marked the screening informed consent form, all screening procedures including the screening informed consent process must be repeated.

4-1.4 Suppose Miss X reports at her first screening visit that she gave birth one week prior to the visit, but she appears to otherwise be eligible and interested in taking part in the study. What should you do?

- Discontinue the current screening attempt and schedule Miss X to return at least 35 days later to re-start the screening process.

Why? Potential participants are ineligible for enrollment in the study if, at the time of the Enrollment Visit, they are within 90 days of their last pregnancy outcome. That is, enrollment must take place on or after the 91st day after the pregnancy outcome date. For Miss X, only seven days have elapsed since her last pregnancy outcome. Since all screening and enrollment procedures must be completed with 56 days, Miss X should be scheduled to return at least thirty-five days (35+56+91) later to re-start the screening process. At that time she will be required to sign another informed consent form for screening.

4-1.5 Suppose Miss X reports at her first screening visit that she had a miscarriage six weeks prior to the visit, but appears to otherwise be eligible and interested in taking part in the study. What should you do?

- Continue the screening process. Schedule Miss X's Final Screening/Enrollment visit (when enrollment may take place) to occur at least 15 (but not more than 56) days later when the participant is post-menses.

Why? Potential participants are ineligible for enrollment into the study if fewer than 90 days have elapsed since their last pregnancy outcome. That is, enrollment must take place on or after the 91st day after the pregnancy outcome date. Forty-two days have elapsed since Miss X's last pregnancy outcome. Therefore she cannot be enrolled until another 49 days have elapsed (42+49=91) so that she is no longer within 90 days of her last pregnancy outcome.

Appendix 4-1 Continued
Screening and Enrollment Scenarios for HPTN 059

4-1.6 Suppose Miss X begins the study screening process on July 1, and that she appears to be eligible after Screening. At the Final Screening/Enrollment Visit, which takes place on July 11, Miss X does not report any STI/RTI symptoms, and otherwise appears to be eligible for the study, but she is diagnosed with bacterial vaginosis (BV) based on Amsel's criteria. What do you do?

- Enroll Miss X in the study on July 11.

Why? Asymptomatic BV is not a study exclusion criterion and does not require treatment per CDC guidelines. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on July 11 despite having been diagnosed with BV that day.

Note: In some cases clinicians may exercise clinical judgment and provide treatment for asymptomatic BV. In such cases, treatment must be completed in order for the participant to be eligible to enroll in the study.

4-1.7 Suppose in Scenario 4-1.6 that, rather than being asymptomatic, Miss X reports abnormal vaginal discharge and is diagnosed with BV based on Amsel's criteria at Final Screening/Enrollment. What do you do?

- Provide treatment for BV per CDC guidelines (ideally single-dose). Schedule Miss X to return to the study site to complete the screening and enrollment process as soon as possible after treatment is expected to be completed and symptoms are expected to have resolved. Assuming treatment was completed and all STI/RTI symptoms have resolved at that time, and the 56-day screening window has not elapsed, continue the screening and enrollment process.

Why? Symptomatic BV requires treatment per CDC guidelines, and all STI/RTI symptoms must be resolved in order for the participant to be eligible to enroll in the study.

4-1.8 Suppose Miss X begins the study screening process on July 1, and that she appears to be eligible after Screening. At Final Screening/Enrollment, which takes place on July 11, Miss X does not report any STI/RTI symptoms, and otherwise appears to be eligible for the study, but yeast is identified on her wet mount. What do you do?

- Enroll Miss X in the study on July 11.

Why? Symptomatic candidiasis requires treatment; however treatment per CDC guidelines is not required in the absence of symptoms. Miss X is free of STI/RTI symptoms and therefore is eligible for the study on July 11 despite the finding of yeast that day.

Note: In some cases clinicians may exercise clinical judgment and provide treatment for asymptomatic candidiasis. In such cases, treatment must be completed in order for the participant to be eligible to enroll in the study.

Appendix 4-1 Continued
Screening and Enrollment Scenarios for HPTN 059

4-1.9 Suppose in Scenario 4-1.8 that, rather than being asymptomatic, Miss X reports genital itching at Final Screening/Enrollment. A curd-like discharge is noted during Miss X's Final Screening/Enrollment pelvic exam and yeast is identified on wet mount. What do you do?

- Provide treatment for symptomatic candidiasis per CDC guidelines (ideally single-dose). Schedule Miss X to return to the study site to complete the enrollment process as soon as possible after treatment is expected to be completed and symptoms are expected to have resolved. Assuming treatment was completed and all STI/RTI symptoms have resolved at that time, and the 56-day screening window has not elapsed, continue the screening and enrollment process.

Why? Symptomatic candidiasis requires treatment per CDC guidelines and all STI/RTI symptoms must be resolved in order for the participant to be eligible to enroll in the study.

4-1.10 Suppose Miss X begins the study screening process on July 1, and that she appears to be eligible after Screening. At Final Screening/Enrollment, which takes place on July 11, a finding involving deep epithelial disruption is observed on pelvic exam, but no other STI/RTI signs or symptoms are present. What do you do?

- Schedule Miss X to return to the study site for a repeat screening pelvic examination as soon as possible after the observed finding is expected to be resolved. Assuming the finding is resolved at that time, and the 56-day screening window has not elapsed, continue the screening and enrollment process.

Why? Deep epithelial disruption is exclusionary for this study.

Note: If syphilis is suspected, also collect blood and perform syphilis serology and other clinical and/or laboratory assessments as appropriate for standard clinical care and follow-up.

4-1.11 Suppose in Scenario 4-1.10 that the observed finding involving epithelial disruption is consistent with a genital herpes (HSV-2) outbreak. What do you do?

- Provide Miss X with treatment per CDC guidelines and schedule her to return to the study site for a repeat pelvic examination as soon as possible after treatment is expected to be completed and the finding involving deep epithelial disruption is expected to be resolved. Assuming the finding is resolved at that time, no STI/RTI symptoms are present, and the 56-day screening window has not elapsed, continue the screening and enrollment process.

Why? Deep epithelial disruption is exclusionary for this study, and genital herpes outbreaks must be treated per CDC guidelines.

Appendix 4-1 Continued
Screening and Enrollment Scenarios for HPTN 059

4-1.12 Suppose Miss X begins the study screening process on July 8, and that she appears to be eligible after Screening. At Final Screening/Enrollment, which takes place on July 28, Miss X reports back pain and painful and frequent urination. What do you do?

- Complete all required Final Screening procedures on July 28.
- Additionally perform dipstick urinalysis. If results indicate urinary tract infection (UTI), provide treatment per site SOP.
- Assuming she meets the study eligibility criteria, enroll Miss X in the study on July 28.

Why? UTI is not exclusionary for this study. As long as all eligibility criteria are met, and Miss X is free of STI/RTI symptoms, Miss X is eligible for the study on July 28 despite having been diagnosed with UTI on that day.

4-1.13 Suppose Miss X begins the screening process on July 18 and appears to be eligible after Screening. Between the initial Screening and Final Screening Visit her lab test results are received and a Grade 3 liver function test result is reported. At Final Screening, which takes place on July 26, Miss X reports that she rarely drinks alcohol, but two days before the initial Screening Visit she attended her sister's wedding and had several glasses of wine. What do you do?

- Complete all required Final Screening procedures on July 26.
- If Miss X appears otherwise eligible for the study, additionally draw blood to repeat her liver function tests.
- Schedule another visit (no later than 56 days after Screening Informed Consent was obtained) to take place when the liver function test results are expected to be available.
- Defer the study (enrollment) informed consent process and all enrollment procedures until the next visit.

Why? Grade 3 lab abnormalities are exclusionary for the study. However, tests may be repeated during the screening process and enrollment may proceed if a non-exclusionary result is documented within 56 days of providing informed consent for screening.

Section Appendix 4-2
Randomization and First Gel Dispensation Scenarios for HPTN 059

4-2.1 On the day of enrollment/randomization, pharmacy staff identify an error on a participant's prescription (e.g., the "date clinic envelope opened" is incorrect). What do you do?

Pharmacy Staff: Return the original prescription to clinic staff and inform them of the error that must be corrected in order for gel to be dispensed.

Clinic Staff: The prescription — both the white original and the yellow copy — must be corrected by clinic staff authorized to complete original prescriptions. Refer to the participant's study chart as needed to determine the correct entries to be added to the prescription. Retrieve the yellow copy of the prescription from the participant's study notebook and record identical corrections on both the white original and the yellow copy. Write identical signed and dated notes explaining the corrections on both the original and the copy. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions. Deliver the corrected white original prescription to pharmacy staff. Retain the corrected yellow copy in the participant's study chart.

Pharmacy Staff: Receive the corrected prescription, verify that all entries are now correct, and give gel per Pharmacy SOPs. File the corrected prescription in participant-specific pharmacy files.

4-2.2 On the day of enrollment/randomization, a study prescription is lost on the way to the pharmacy. What do you do?

Clinic Staff: Make a photocopy of the yellow clinic copy of the prescription and obtain another original authorized prescriber signature and signature date on the photocopy. Document the occurrence and action taken in a signed and dated chart note. Deliver the signed photocopy of the prescription and a photocopy of the chart note to the pharmacy. The documents may be delivered to pharmacy staff by the participant or by study staff. In this case, because the prescription is a signed photocopy, it is recommended for clinic staff to explain the situation to pharmacy staff.

Pharmacy Staff: Give gel per the new HPTN 059 prescription. File the signed photocopy of the prescription and the photocopy of the clinic staff note in participant-specific pharmacy files.

Note: These same steps would be taken if a prescription were to be lost by a clinic staff member or product runner.

4-2.3 Two days after receiving her first set of carton(s) of gel, a participant returns to the clinic and reports that she has tried to use the tubes and applicators (which she has brought with her) but the tubes seem empty. What do you do?

Clinic Staff: Determine if the tubes and applicators are either defective or if the participant is not following the directions for study gel insertion properly. To determine if the participants if following the study gel insertion instructions properly, review the instructions with the participant and ask the participant if she had any problems at any of the steps.

If it is determined that the participant is not following the instructions properly, discuss the participant's current understanding of how to use the tubes and applicators and provide refresher instruction is needed. Then ask the participant to try to insert the gel again in a private on-site location (using one of the tubes and applicators she brought back with her; give her a suitable container in which to place the tube and applicator before and after use).

Once the refresher instructions are provided, and the clinic staff is confident that the participant will be able to insert the gel correctly, count the number of the tubes and applicators the participant has remaining and refer to the Study Gel Re-supply Worksheet to determine if the participant needs additional supplies. If the participant needs additional supplies, document in the participant's charted note, and attach copy of signed, dated chart note to an HPTN 059 Study Gel Request Slip for supplemental study gel supplies. Refer/escort the participant to pharmacy staff for supplemental gel supplies with the Study Gel Request Slip and copy of signed, dated chart note.

Dispose of the used/and or tubes and applicators, and ensure event is completely document in the participant's chart note.

- Pharmacy Staff: Dispense supplemental study gel supplies per Pharmacy SOPs.

4-2.4 Following on from Scenario 4-2.3, after you have reviewed the study gel insertion instructions with the participant, you determine the participant was inserting the study gel correctly, but the tubes and applicators are defective. What do you do?

Clinic Staff: If the participant needs additional supplies, document in the participant's charted note, and attach copy of signed, dated chart note to an HPTN 059 Study Gel Request Slip for supplemental study gel supplies. Refer/escort the participant to pharmacy staff for supplemental gel supplies with the Study Gel Request Slip, copy of signed, dated chart note, and defective study supplies.

Pharmacy Staff: Once a Study Gel Request Slip is received, give replacement supplies according to Pharmacy SOPs.

Store the tubes and applicators collected from the participant in a designated "quarantine" area for returned defective study product. Do not attempt to examine the applicators. Inform the DAIDS Protocol Pharmacist immediately; the Protocol Pharmacist will inform the Pharmaceutical Co-Sponsors, HPTN CORE Protocol Specialists. Follow any further instructions provided by the DAIDS Protocol Pharmacists and document all further action

taken.

Pharmacy Staff/All Outcomes: Inform clinic staff of the outcome/resolution of the participant's report and provide written documentation for inclusion in the participant's study chart (e.g. a photocopy of signed and dated pharmacy staff notes or a separate signed and dated note or memo to file). Be sure the documentation provided does not contain coded information related to the participant's random assignment to study gel.